

PHYSIOLOGICAL
PAPERS ∴ ∴ ∴
H. NEWELL MARTIN

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Memoirs from the Biological Laboratory

OF THE

JOHNS HOPKINS UNIVERSITY

III

PHYSIOLOGICAL PAPERS

BY

H. NEWELL MARTIN

Dr. Sc., University of London; A. M., University of Cambridge; M. B., London University; M. D. (Hon.), University of Georgia; late Fellow and Lecturer in Christ College, Cambridge; Fellow of University College, London; Fellow of the Royal Society; Professor of Biology, Director of the Biological Laboratory, and Editor of the Studies from the Biological Laboratory, Johns Hopkins University, 1876-1894, and Professor of Physiology in the Medical Faculty of the same

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Professor Henry Newell Martin held the chair of Biology in the Johns Hopkins University, from 1876 to 1893—a period of seventeen years. To the great regret of all his friends, he was compelled by ill-health, in the summer of 1893, to resign his professorship and return to England.

As a teacher, lecturer and investigator Dr. Martin has exerted a deep influence upon the character of biological instruction in this country; the development of experimental research in animal physiology has, however, been the object of his most earnest labor, and in this department of biology he has made brilliant additions to our literature.

In recognition of the value of his work and as a token of their affection and esteem for him, his friends and pupils have undertaken the publication of this collection of his papers. The committee entrusted with the preparation of the volume have selected from Professor Martin's writings some of his public addresses and all of his contributions to experimental physiology made during his connection with the University. Many of the publications of his pupils inspired by him might have been included in the collection, but it is thought better to restrict it to those papers which appeared under his own name.

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In the arrangement of the papers in this volume it has been thought better not to follow a strict chronological order, but to group together those bearing upon similar topics. The contributions to the physiology of circulation have been given precedence; these are followed by the researches upon the physiology of respiration, and these by the public addresses. In each group the papers follow in chronological order.

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I.

A NEW METHOD OF STUDYING THE MAMMALIAN HEART.

With Plate 1.

[*Studies from the Biological Laboratory of the Johns Hopkins University,*
Vol. II, p. 119, 1881.]

In the course of some experiments made by me in conjunction with Dr. W. T. Sedgwick, on blood pressure in the coronary arteries of the heart, the fact was impressed upon me that the mammalian heart is no such fragile organ as one is usually inclined to assume, but possesses a very considerable power of bearing manipulation. On the other hand, I knew of various unsuccessful attempts to isolate the mammalian heart and study its physiology apart from the influence of extrinsic nerve centres, in a manner more or less similar to the methods so frequently used for physiological investigations on the heart of a cold-blooded animal; the mammalian heart, however, always died before any observations could be made on it. Thinking over the apparent contradiction, it occurred to me that the essential difference probably lay in the coronary circulation; in the frog, as is well known, there are no coronary arteries or veins, the thin auricles and spongy ventricle being nourished by the blood flowing through the cardiac chambers, but in the mammal the thick-walled heart has a special circulatory system of its own and needs a steady flow through its vessels, and cannot be nourished (as appears to have been forgotten) by merely keeping up a stream through auricles and ventricles. The greater respiratory needs of the heart of the warm-blooded animal also needed consideration; the lungs ought either to be left connected with it, or replaced by some other efficient aërating apparatus; if entirely separated from the central nervous system there seemed no need to replace the natural lung by an artificial one, and, though I hope ultimately to do this, my work hitherto has been confined to the study of heart and lungs living together, when all the rest of the body of the animal was dead. Under such circumstances, with uniform artificial respiration, the lungs may be regarded as purely physical organs adapted for gaseous diffusion; and probably better for this purpose than any substitute which could be constructed.

My first experiments were made with cats. The animal was narcotised with morphia, tracheotomised, and a cannula put in the left carotid. Then the thorax was opened (artificial respiration being started), the innominate artery tied beyond the origin of the left carotid but proximal to the point where the right subclavian and right carotid separate; the left subclavian was ligatured near its origin; and the aortic arch tied immediately beyond the origin of the left subclavian. Finally, the superior and inferior cavæ and the root of one lung were tied; the cannula in the left carotid was connected with the manometer of the kymographion, and tracings taken in the usual manner. Under these circumstances the course of the blood was—left auricle, left ventricle, aortic arch and the ligatured arterial stumps connected with it, the coronary vessels, the right auricle, the right ventricle, the pulmonary circulation through one lung, and back to the left auricle. All circulation was cut off from every organ in the body except heart and lungs; the brain and spinal cord soon died, the muscles became rigid, and kidneys and liver had no longer any physiological connection, either through the nervous system or the blood, with the heart; which, though still in the body, was physiologically isolated from everything but the lungs; yet as my preliminary experiments showed (Johns Hopkins University Circular, No. 10, p. 127, April, 1881), the heart went on beating with considerable force and regularity for more than an hour.

The method, however, still left much to be desired; I wanted the heart alive much longer; a means of keeping it at a uniform temperature; a method of renewing the blood which, either because clogged with waste products usually removed by the kidneys or other organs, or because certain nutritive materials in it were used up, ceased to be efficient in keeping the heart alive after a certain time; and opportunity to run blood, to which various substances had been added, through the heart from time to time in order to study their action upon it.

After several attempts the apparatus represented in Plate 1 was devised, and has been found to answer admirably; with it I have kept a heart, isolated physiologically from everything but the lungs, beating with beautiful regularity for more than five hours, and have no doubt I could keep it considerably longer were that necessary.

In the plate the heart is represented very diagrammatically and of hugely disproportionate size; the pulmonary vessels also are entirely omitted, as they are not interfered with in the experiment. At first I thought the immense disproportion in capacity between the complete

pulmonary system of vessels and the systemic circulation reduced to only its coronary portion would injure the working of the heart, and I tied up, as above stated, the root of one lung and sometimes one or two lobes of the other; but I have since found that this is quite unnecessary; the left auricle takes only what it wants, no matter how much blood is accumulated in the lungs, and the circulation is thus confined to the quantity of blood which under a given aortic pressure is sent through the coronary system in a given time.

The course of an experiment is as follows: Tracheotomy having been performed, each pneumogastric nerve is divided in the neck; this is, I find, of importance as saving the heart from the effects of powerful dyspnœic inhibition when subsequently all the cerebral circulation is cut off. A cannula, *p*, is then placed in the left carotid, *o*; and another, *s*, in the right carotid, *r*; the purpose of these will be mentioned presently. Next the first pair of costal cartilages and the piece of sternum between them are resected, artificial respiration started, and the internal mammary arteries found and ligatured where they pass forwards between the apices of the lungs. The sternum and the sternal ends of the ribs are then cut away down to the diaphragm, and if the day is cold a cloth soaked in moderately hot water laid over the posterior half of the chest so as to keep lungs and heart warm, care being taken that it does not touch the pericardium; this hot damp cloth is renewed from time to time as necessary; on a warm day it may be omitted.

Next the superior cava is pushed aside and the right subclavian artery, *w*, clamped and opened. The bulb of a slender thermometer, *a*, is then placed in the vessel and, the clamp being removed, is pushed down into the innominate trunk and tied so as to keep it there. This gives the temperature of the blood flowing through the heart, which cannot be deduced accurately from the temperature of the chamber in which the apparatus is placed; partly because the blood warms and cools more slowly than the air in the box, and partly because in its circuit through the lungs it is cooled. A very small twig given off from the innominate trunk to the anterior mediastinum is also tied. Next the left subclavian, *m*, is isolated and a cannula, *x*, placed in it; and the aortic arch, *l*, tied just beyond the origin of the left subclavian. When the subclavians and aorta are tied (the carotid flow being already stopped) anæmic or dyspnœic convulsions occur, and arterial pressure rises very high, as evidenced by the great size to which the stumps connected with the aortic arch become distended; to obviate this strain on the heart,

the aortic arch is tied as quickly as possible after putting the cannula in the left subclavian, and before the dyspnœa is extreme a large quantity of blood drawn off through the cannula, *s*, in the right carotid; when what appears sufficient is drawn the screw-clamp *u* is tightened up again. Finally the inferior cava, *e*, is ligatured, and the azygos vein, *f*; and a cannula, *h*, put in the superior cava, *g*. This finishes the operative procedure.

To get rid of the blood now present in the heart and lungs, which would be apt to clot in the cannula during a subsequent prolonged observation, and to replace it by defibrinated blood, of which about two litres are obtained from other dogs before the experiment, is the next step. The cannula *h* is filled with whipped blood and connected with a funnel containing the same warmed to 35° C.; the clamp *t* on the right carotid is then again opened and from 300 to 400 cc. of defibrinated blood run through the heart and lungs—in by the superior cava and out by the carotid—washing out and replacing the blood previously present; the blood drawn is whipped and strained and added to the stock on hand. The supply should be slow and sent in under a pressure equal to that exerted by a column of blood about 20 centimetres in height. The carotid is then again clamped and the vena cava a second or two later, after the heart and lungs have filled up with blood. The funnel is now removed and the heart, still lying in the chest, is ready for transference to the chamber in which it is to be kept warm and moist and fed with fresh defibrinated blood.

This chamber consists of a box five feet long, three high, and two and a half wide. It has no floor; has one wooden end, *I*; a wooden back; a glass front; a glass roof, *K*; and a glass end, *L*. The front can be entirely removed and has also a door in it through which matters can from time to time be arranged inside and temperatures read off without removing the whole front. The chamber rests on a galvanized iron trough, *DD*, which contains about an inch and a half of water. In it is a Bunsen's regulator connected with the burners, *CC*, and serving to maintain a uniform temperature in the interior. In the chamber about an hour before the experiment are placed the glass cylinders 27 and 28, each containing about 800 cc. of fresh whipped and strained dog's blood, which has thus time to attain the temperature of the interior of the box.

All being ready, the front of the chamber is removed and the dog stretcher *GG*, having on it the dead body of the dog with the living heart

and lungs, is put in. The heart alone is indicated in the diagram to make description of its connections easier. The cylinders 27 and 28 are elevated on a block at the anterior end of the stretcher, so that their lower ends are ten or twelve centimetres above the auricular end of the heart. These cylinders are Mariotte's flasks. Each is closed air-tight at the top by a cork through which four tubes pass; one tube in each case (9 and 12 respectively) allows air to enter from the interior of the chamber and reaches to near the bottom; another (5, 6) dips a little deeper into the blood and acts as a syphon to draw it off. The remaining tubes (7 and 10, 8 and 11, respectively) only reach a short way through the cork. Each has on its upper end a bit of rubber tubing which can be closed air-tight by a clamp, and is so when the cylinder is in use. These short tubes are for filling the reservoirs; when one cylinder is nearly empty, as for instance 27 in the diagram, the clamp, 2, on the tube leading from it to the heart is screwed up, and the communication between the heart and the other reservoir opened; while this second one is feeding the heart the first is refilled by opening the clamps 18 and 17, putting the funnel 19 on the rubber tubing of 11, and refilling the reservoir through it; as the blood enters the air escapes through 10; when the cylinder is filled the clamps 17 and 18 are again screwed tight and the cylinder is again ready for use long before its fellow has emptied.

The syphons leading from each Mariotte's flask meet in the Y-piece *z* from which passes the rubber tubing *i*. As soon as the animal is placed in the chamber this bit of tubing is filled with blood by opening its connection with one of the reservoirs, and is immediately slipped over the end of the cannula, *h*, in the superior cava, from which the clamp is removed: the heart is thus steadily supplied with blood from each reservoir in turn. The outflow tube, *q*, passes from the left carotid, *o*, which is not used for the preliminary bleeding and washing out which, with the object of avoiding any clotting in the left, are done through the right carotid as above described; now that there is only defibrinated blood to deal with there is no longer any danger of such clotting. Over the cannula, *p*, is slipped one end of the rubber tube, *q*, which leads to the glass tube 21, which passes through the wooden end of the box and has on it a stop-cock, 22, beyond which the tube curves round and reënters the box. By means of the stop-cock the rate of irrigation can be regulated without opening the chamber; the blood which flows through is received in the vessel, 24, which is set aside within the box and replaced by another from time to time as necessary, until one of the Mariotte's flasks

needs refilling. In this way the blood being nearly always inside the chamber does not get a chance to cool more than a degree or two, and so has ample time to heat up again to the proper point while the other Mariotte's flask is emptying. The rate of flow permitted is usually a pretty rapid dropping; but if a low arterial pressure is desired the stop-cock, 22, is opened wide; if a higher it is more closed. Even a slow dropping keeps the heart well alive for a long time; if signs of feebleness come on, all that is needed is to open the stop-cock wide for a few seconds and thoroughly renew the blood in the heart.

Arterial pressure and the pulse curves are obtained from the mercurial manometer 26. This, by means of connecting tubes, filled with sodic carbonate solution in the usual manner, is attached to the cannula *x* in the left subclavian.

All the connections having been made, the front is replaced on the chamber and henceforth the heart beats on in it without disturbance, except as from time to time a small door is opened to change the receptacle 24, or take out blood to refill one of the Mariotte's flasks and change the one connected with the heart by opening or closing the clamps 1 or 2, or note the temperature of the thermometer *a*.

The description of the various connections to be made after the animal is placed in the chamber takes some time, but the whole thing is done in two or three minutes. While the front of the chamber is out the air in it cools considerably, but the blood of course much less on account of its high specific heat, and in a very few minutes, while one waits for the heart to get uniform and to be sure that brain and spinal cord are dead, all inside is again at a uniform temperature and a series of observations can be commenced. Before commencing these I always wait until all signs of reflex excitability are lost and the muscles begin to exhibit rigor; this occurs at latest in half an hour after ligaturing the various arteries. Sometimes Traube's curves are seen for a few minutes after the animal is placed in position, showing that the medulla is not quite dead; but they very soon pass off, never to return, though when the heart begins to die something simulating them (to which I will return later) usually occurs.

It is, I think, clear that by this plan of work the study of the physiology of the mammalian heart is made possible to an extent never before attainable; I have now made a considerable number of observations which show that for at least four hours and often for considerably longer, great regularity and power in the heart's beat can be maintained.

I give below in tabular form the successive observations as to pressure in the subclavian and pulse rate made in two experiments, which show the perfect availability of the method. To investigate the direct action of any drug on the heart one would have only to inject it by a hypodermic syringe into the cardiac end of the tube *i*, as in the usual manner of injecting curari into a vein. By altering the temperature of the chamber one can readily study the effect of various temperatures on the pulse rate, arterial pressure being kept at a given level while the tracings (at intervals of five or ten minutes) are being taken, by altering the outflow through the stop-cock, if necessary; between the readings a uniform flow is kept up irrespective of arterial pressure. By keeping the temperature constant and altering the stop-cock the direct influence of various arterial pressures on the pulse rate can be readily studied. On these two latter points I have already made a number of interesting observations, which are not, however, yet quite ready for publication. The chemical products of muscular work apart from those eliminated by the lungs must also accumulate in the blood which has flowed round and round the beating heart for hours, and probably can there be examined better than in any other organ at present at our disposal. It seems also to me practicable to unite a given organ, say kidney or liver, with the heart and keep it alive for study, but this I have not yet tried. At any rate it is clear that a large field for investigation of various points of great interest is made available for study under much more favorable circumstances than hitherto.

When the heart begins to die the first symptom is an irregular rhythm which cannot be removed by free irrigation with the blood in the reservoirs. Whether this is immediately due to changes in the heart itself, or to the consumption of food materials in the stock of blood, or to the accumulation in it of wastes usually removed by the kidneys or other organs I cannot at present state. Whether it be due to the first of the above causes could readily be decided by taking an entirely fresh stock of defibrinated blood. The irregularity manifests itself by a large beat followed by three or four smaller ones, and so on for more than an hour. Then the small beats become feebler and feebler, and, arterial pressure being consequently very low, the pulse due to the more powerful beat very conspicuous. Finally the large beats alone remain, and they gradually become less and less until they disappear. In its earlier stages the phenomenon has an interesting resemblance to the secondary rhythm observed in the frog's heart under certain circumstances; it is what I

referred to above in stating that late in the experiment something simulating Traube's curve is often seen.

For the guidance of those who may repeat the experiment, I may add that the thing most to be avoided is sending blood into the superior cava too fast or under too high a pressure; this is far more fatal than considerable cooling or delay.

The following tables give the results of two experiments. In each case the number indicated in the column headed "pressure" is the pressure in millimetres of mercury indicated by the manometer connected with the left subclavian artery. The numbers in the column headed "pulse" give the number of heart beats per minute. Temperatures, when given (Table II), are not accurately those of the heart or blood, but those of the chamber in which the heart lay. The introduction of a thermometer into the innominate trunk I have only used in later experiments on the influence of temperature changes on the pulse rate, when an accurate knowledge of temperature was essential; in the experiments given here the point I had in view was merely to determine whether an isolated heart could be kept alive long enough for study; and accuracy as regards temperature readings within a degree or two was not essential.

Table I records the first experiment, which showed me that the end I had in view was really attainable, and is given partly, perhaps, because I have a special interest in it on that account, but chiefly because it illustrates how well the heart will live under very rough experimental conditions. At the time when it was made I had not arranged any warm chamber, and the heart was simply warmed in the roughest manner by inverting a tin pan over the body of the dog and putting a Bunsen's burner under this, with some wet cloths to keep the atmosphere moist. From time to time the gas was turned down or up as I thought the temperature round the heart was too high or too low, but no thermometer readings were taken, and the temperature no doubt varied very much in the course of the experiment. At this time also the use of the Mariotte's flasks had not been thought of: from time to time, as the heart seemed weakening, fifty cubic centimetres of whipped blood were run in by the vena cava and an approximately equal bulk removed through the carotid. The numbers given, therefore, as to pulse rate and arterial pressure have little or no value; and the whole experiment simply serves to show with what rude appliances the isolated heart can be kept at work for a long time when the coronary circulation is maintained.

TABLE I.—EXPERIMENT OF APRIL 1, 1881.

Time. P. M.	Pressure.	Pulse.	Remarks.
1 h. 35'			Finished tying up all the vessels but those of the pulmonary and coronary circuits.
1 h. 40'	68	96	
2 h. 20'	74	87	
2 h. 22'			Fresh blood run in.
2 h. 23'	96	104	
2 h. 30'	93	102	
2 h. 37'	118	96	
2 h. 40'	80	93	
2 h. 50'	96	100	
3 h. 04'	60	100	Fresh blood run in at 3 h. 3'.
3 h. 21'	86	96	
3 h. 28'	104	42	Cold blood run in at 3 h. 27'.
3 h. 50'	32	96	
3 h. 51'			Fresh warm blood run through.
3 h. 52'	92	112	
4 h. 06'	41	88	
4 h. 13'	25	80	
4 h. 15'			Fresh warm blood run through.
4 h. 16'	92	86	
4 h. 29'			Fresh warm blood run through.
4 h. 30'	92	79	
4 h. 39'			Fresh warm blood run through.
4 h. 40'	90	88	
4 h. 47'	56	88	
4 h. 59'			Fresh warm blood run through.
5 h. 00'	76	86	
5 h. 09'	43	96	
5 h. 10'			Fresh blood taken from another dog and not used before in the course of this experiment, run through.
5 h. 18'	140	88	
5 h. 23'	58	72	
5 h. 26'			Fresh blood.
5 h. 29'	116	83	
5 h. 33'	52	76	
5 h. 35'			Fresh blood.
5 h. 40'	60	82	
5 h. 44'			Fresh blood.
5 h. 45'	102		Chronograph pen out of order, so the pulse rate cannot be given.
5 h. 48'	76		
5 h. 53'			Fresh blood.
5 h. 55'	92	92	
6 h. 00'	37	88	
6 h. 02'			Fresh blood.
6 h. 03'	61	98	
6 h. 11'			Fresh blood.
6 h. 14'	88	92	
6 h. 20'	42	88	
6 h. 22'			Fresh blood run in ; none drawn off.
6 h. 24'	118	98	
6 h. 30'	32	97	
6 h. 35'	24	96	
6 h. 36'			Fresh blood run in ; none drawn off.
6 h. 38'	118	100	
6 h. 41'	28	84	
			The beat immediately afterwards became very irregular, and ceased finally at 7 h. 10'.

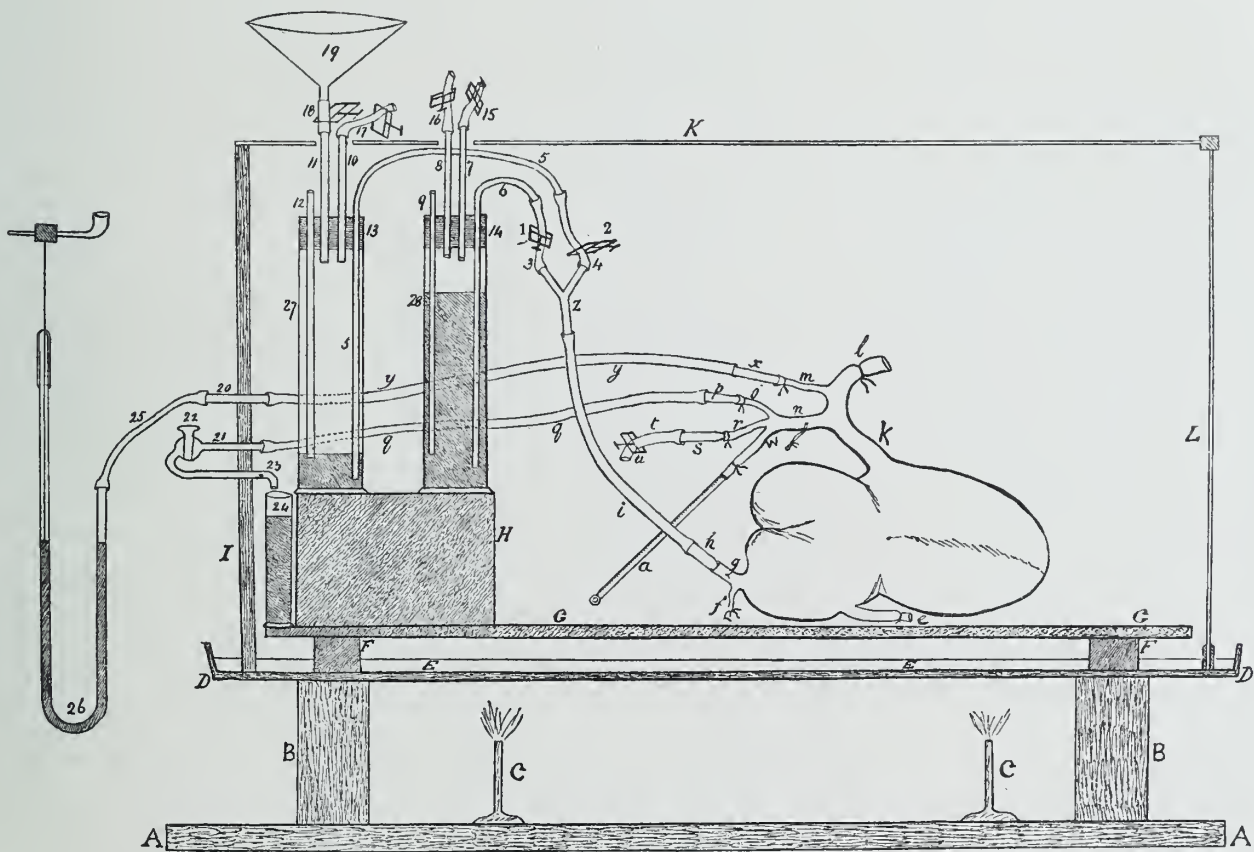
The above experiment, as already stated, justifies no conclusions except that an isolated mammalian heart can be kept beating for several hours. It, however, suggests (and subsequent experiments, which I hope shortly to publish, confirm) that the pulse rate of the isolated heart is very independent of arterial pressure, though, as no accurate temperature observations were made in this case, the experiment by itself is not worth much in that respect.

TABLE II.—EXPERIMENT OF MAY 26, 1881.

Time. P. M.	Temp. in degrees F.	Pressure.	Pulse.	Notes.
1 h. 50'				All vessels tied but those of the coronary and pulmonary circuits. Then 150 cc. of warm whipped blood sent through the heart in order to wash out the blood already in it and in the lungs.
2 h. 05'				Animal removed to warm chamber and the irrigation started from the Mariotte's flasks and maintained thenceforth.
2 h. 15'		72		Pulse rate not known, as the chronograph was not working.
2 h. 45'	95	72	92	
3 h. 00'	99	86	118	
3 h. 15'	98	87	118	
3 h. 55'	99	90	120	
4 h. 15'	99	91	120	
4 h. 35'	100	87	118	
4 h. 50'	100	86	120	
5 h. 10'	100	68	117	
5 h. 45'	100	64	117	
6 h. 00'	100	60	118	
6 h. 15'	99	56	117	Arterial pressure now began to fall markedly, and while a fresh supply of blood was being obtained from another dog (that in use having already circulated round the heart many times and being presumably full of wastes) the organ ceased to beat at 6 h. 45'.

The experiment described in Table II was made in the warm chamber described in the preceding pages and with the Mariotte's flasks, giving a uniform instead of the intermittent supply of fresh blood used in the experiment of Table I. It is one of a number which all show the great regularity which can be obtained for some hours in the heart's work under such circumstances; and hence the possibility of readily observing the influence on its activity of various conditions and of drugs: in other words, it indicates that the separated organ is in a fit condition for physiological or therapeutical experiment.

During the earlier part of the above experiment (from 2.15 to 3.00 P. M.) the chamber and its contents were considerably cooled in conse-



quence of one of the Mariotte's flasks being out of order and necessitating the keeping open of the doors, for its repair. When this was accomplished, we find for the subsequent two hours (3 h. 00' to 4 h. 50') a very remarkable uniformity in the heart's work. Arterial pressure only varies between 86 and 91 mm. of mercury, and the pulse rate between 118 and 120 per minute. Probably under no conditions would a heart still connected physiologically with the rest of the body display so great a uniformity in its activity for so long a time. The pulse, it will be seen, still remained very regular to the end of the experiment, although arterial pressure fell; this again illustrates the slight influence exerted by aortic pressure upon the rhythm of the isolated heart.

II.

THE INFLUENCE UPON THE PULSE RATE OF VARIATIONS OF ARTERIAL PRESSURE, OF VENOUS PRESSURE, AND OF TEMPERATURE.

[*Transactions of the Medical and Chirurgical Faculty of Maryland*, p. 203, 1882.]

Last year I had the honor of laying before the members of the Medical and Chirurgical Faculty of Maryland a brief account of a new method of studying the physiology of the heart of the mammal, which rendered it possible to separate the organ entirely, both as to nervous connections and circulation, from all remaining parts of the body except the lungs. Since then I have been mainly occupied with a study of the influence of various conditions upon the pulse rate of the so isolated heart. Having been invited by your Executive Committee to address you to-day, I have thought that possibly some account of these experiments might interest you, as the pulse-rate is so valuable an indication in many forms of disease. A practitioner may, nowadays, when making a professional visit, omit to say "Put out your tongue" without being thought to have neglected his duty, but the family doctor who fails to feel his patient's pulse seriously risks losing the confidence of mater-familias.

Apart, however, from the whims of those with whom we have to do, there does remain the primary and universally acknowledged fact that in many cases the pulse-rate is a most valuable factor in forming a diagnosis, making a prognosis, or deciding upon a treatment. I therefore venture to hope that what little I may be able to add to your knowledge of the causes which influence the rate of beat of the heart may be not unwelcome.

As the method of work has been somewhat improved since I last addressed you, it is necessary to begin with some brief account of it. The guiding idea is to prevent all circulation through any part of the body of a warm-blooded animal but the heart and lungs. From want of blood, brain, spinal cord and sympathetic ganglia very soon die, and so the heart is liberated from the control of nerve centres outside of itself. In the second place, the heart, thus isolated, receives only blood of

constant composition and known temperature, sent into it under readily controlled conditions. The animal having been tracheotomized, placed under curari, morphia or chloroform, the common carotid arteries are exposed, tied, and cannulas placed in their central ends. The pneumogastric nerves are divided in the middle cervical region. The next step is to expose the heart and great thoracic blood-vessels by opening the thorax. To this end, artificial respiration, if not already employed, is started, the top of the sternum with the cartilages of the first pair of ribs is resected, and the cephalic end of the anterior mediastinum exposed. On its sides the internal mammary arteries are readily found, coursing forward from the subclavian to the sides of the sternum, and ligated. This having been done, the whole front and sides of the thorax are cut away to within an inch or two of the vertebral column. In most cases this leads to a little bleeding; sometimes a few of the intercostals spirt vigorously and require torsion or a hard pinch by finger and thumb or a pair of forceps to stop the bleeding.

The next steps have for their object to close all paths of the greater circulation but those through the coronary system. Before describing them it will be necessary to indicate some points in which the anatomy of the great vessels of the dog differs from that of the corresponding trunks in man.

From the arch of the aorta in the dog arise (1) the two coronary arteries; (2) the brachio-cephalic; (3) the left subclavian. The brachio-cephalic gives off, first, the left carotid, and then divides into the right carotid and the right subclavian. Beyond the arch the usual bronchial and intercostal branches are given off by the thoracic aorta.

The first step after opening the chest is to tie the right subclavian below the origin of its first branch. The two carotids are already blocked by cannulas, as above stated. Next a ligature is put around the left subclavian below its first branch. Now all blood is cut off from the head save such as reaches it by anastomoses from vessels in the spinal cord, and, consequently, little arterialized blood reaching the medulla, the animal, unless curarized, exhibits dyspnœic symptoms, due to the deficiency of oxygenated blood in its respiratory centre.

As has been noted by other observers, however, the dog's medulla gets a good deal of blood by other roads than along the carotids and subclavians, so that after ligating all four arteries the dyspnœa does not pass on into the convulsions of a more extreme asphyxia, as it does later when the thoracic aorta also is closed.

Next a metal cannula, curved at one end so as to present a long limb and a short limb at right angles to one another, is put into the aorta. For this purpose a ligature is loosely placed around the vessel just beyond its arch, and a stout clamp put on it further down in the thorax. The thoracic aorta is then opened just above the diaphragm and the free end of the long limb of the cannula introduced. The clamp is removed, and the cannula, which is of such size as to barely fit into the aorta, is pushed along till its end reaches the aortic arch, when the ligature above mentioned is tied around it. The result of this is obviously that all circulation through the systemic arteries, except the coronaries, is blocked. The heart is the only organ now receiving blood from the left ventricle.

The next stage is to tie up the systemic veins leading to the right auricle. A ligature is quickly put around the inferior vena cava above the diaphragm; another around the vena azygos near its entry into the superior cava, and then the superior cava is ligated on the cardiac side of its last tributary. On the cardiac side of this ligature a large tube is introduced, which tube is in communication with a flask filled with defibrinated dog's blood, or the same diluted with one-third its bulk of 0.7 per cent. sodium chloride solution, or filled with defibrinated calf's blood.

The flask having been placed in connection with the heart, the carotids are opened, and all the blood present previously in the heart and the lungs of the dog is washed out and replaced by defibrinated blood. While this is being done a thermometer is placed in the left subclavian artery.

The animal (none of whose body but heart and lungs now has any circulation) is next transferred to a warm, moist chamber. The superior cava is connected with a Mariotte's flask, from which defibrinated blood under a known and easily controlled pressure enters the vein and thence the right auricle.

The aortic cannula is connected with a long rubber tube having at its distal end a bent glass tube, from which the blood forced out by each contraction of the left ventricle is poured into a funnel; from this funnel a tube leads to a Mariotte's flask exactly like that in connection with the right auricle. The blood taken by the right heart from one Mariotte's flask is thus pumped by the left heart into another: when the first is empty, by altering the position of a couple of stop-cocks the course of the blood is changed. The heart then receives it from the second Mariotte's flask and pumps it back into the first; and by altering the stop-

cocks from time to time as necessary, the blood circulates time and again through the heart as often as desired.

Under these circumstances the heart is under conditions allowing of accurate experiment with respect to various points.

Keeping the Mariotte's flasks at a constant level and the blood in them at a constant temperature, we can alter arterial pressure by elevating or lowering the exit point of the tube connected with the aorta. Keeping the level of the outflow of the aortic tube constant, we can maintain an approximately constant resistance to the systole of the left ventricle, while we alter venous pressure (*i. e.* pressure in the right auricle) by raising or lowering the supplying Mariotte's flask; and, finally, keeping venous pressure and arterial resistance constant, we can change the temperature of the blood supplied to the heart, and study by itself the influence of changes of temperature on the pulse-rate.

Let us first consider the effect of changes of arterial pressure on the pulse; a matter hitherto in much dispute.

Marey showed that in animals whose hearts were not separated from the influence of extrinsic nerve centres, a rise of arterial pressure slowed the beat. Upon this he founded the very neat, but unfortunately incorrect theory that when the heart had to pump against greater aortic pressure, each ventricular systole took longer and the pulse-rate was slowed.

Subsequent work proved that Marey's experimental results did not justify the conclusions which he drew from them. Increased pressure in the brain-case was shown to slow the beat of the heart quite independently of any general rise of aortic pressure; for instance, injecting a small quantity of liquid through a hole trephined in the skull greatly diminishes the pulse-rate although general arterial pressure is not raised.

This phenomenon (that of a slower pulse with increased cerebral pressure) is well known to the members of this Faculty as one of the concomitants of apoplexy, due to an effusion of liquid within the brain chamber.

Experiment on the lower animals has, however, proved that increase of pressure in the skull cavity does not slow the heart's beat if the pneumogastric nerve be previously cut. Hence Marey's experiments, in which with undivided pneumogastriacs the general blood pressure, including that in the skull cavity, was raised, really prove no direct mechanical action of such rise of blood pressure on the heart's rate of beat. The increased tension in the brain-case may have excited the vagus centres, and through them slowed the pulse.

Further, it has been proved that there exists in the medulla oblongata, alongside of the cardio-inhibitory centre, which is excited by increased arterial pressure in the skull cavity, a cardio-accelerator centre—still but little investigated—which seems to be stimulated by diminished arterial tension in the arteries of the brain. When the aorta is clamped beyond its arch, arterial pressure in the vessels of the fore-limbs and of the brain is increased and the cardio-inhibitory centres excited. When, on the other hand, the common carotids are ligated, general arterial pressure is raised, but pressure in the brain is diminished. This diminution of intracranial arterial pressure excites the centre in which the cardio-accelerator nerve fibres originate, and from which they pass down the cervical spinal cord and thence through the sympathetic chain to the heart.

We thus see that Marey's conclusion that increased arterial resistance mechanically and directly slows the heart-beat has no logical foundation. If the pneumogastrics be intact and we raise arterial pressure by clamping the abdominal aorta, we slow the heart; but such an experiment increases pressure in the brain arteries, and this indirectly slows the heart-beat. If aortic pressure is raised by clamping the common carotids while raising the general pressure in the systemic arteries, we quicken the pulse, apparently because pressure in the brain arteries is diminished and this excites the centre of the accelerating heart nerves. To find what direct influence variations of pressure have on the pulse-rate we must first separate all nerves reaching the heart from outside.

Whenever any experiment is made in vascular physiology, arterial pressure is nearly certain to be altered. If we stimulate a sensory nerve, for example, we find a rise of blood pressure, and usually a change in the rate of beat of the heart. Whether stimulating the nerve only affects the pulse-rate through the changed arterial pressure, cannot be decided until we study the influence of change of pressure pure and simple. If that has no effect, then the sensory nerve must reflexly, in some other way, control the pulse-rate.

In fever, arterial tension is changed and pulse-rate altered. Is the alteration in arterial pressure the cause of the quicker pulse, or is some other agency at work? If a tourniquet be placed on the abdominal aorta, will the resulting change of aortic tension directly affect the pulse-rate? If not directly, how does it affect it, granted that the change of arterial pressure does exert some influence upon the pulse-rate?

Such questions as these, and many others, can only be answered when changes in arterial pressure are produced after all action of the extrinsic heart nerves has been excluded. From its physiological and pathological importance, many experimenters have been at work on the matter. By cutting the vagi, and also the branches which pass from the inferior cervical and the first dorsal sympathetic ganglia to the heart, we separate the organ from all connection with nerve centres outside itself. Then, it has been assumed, we have practically an isolated heart to deal with. But the results of experiments in the hands of different observers, and even of the same observer, have been so contradictory that it is clear there was still some unrecognized source of error. When observers like Ludwig, Heidenhain, v. Bezold, Nawrocki and Tschirjew, working with care, describing their apparatus in detail, so that no flaw is apparent, get at absolutely contradictory results (as that a rise of aortic pressure has no influence on the pulse-rate; that it invariably slows it; that it invariably quickens it; that it sometimes slows and sometimes quickens it), it becomes pretty clear that there is an unrecognized defect somewhere in the method of experiment. This defect is, I am convinced, largely due to a failure to pay proper heed to the temperature of the blood sent through the heart, a matter which has been quite ignored in most cases, or at least by no means properly taken account of.

It would only weary you to go into detail as to how this factor comes into play in different cases; but I may illustrate it by a reference to the work of v. Bezold, whose untimely death cost physiology so much. In the remarkable series of works on the physiology of the heart which were carried on in his laboratory in the last year or two of his life, there is one research by v. Bezold himself in conjunction with Dr. Stezinsky. It is titled, "On the Influence of Intracardial Pressure on the Frequency of the Heart-beat."

Taking weakly curarized rabbits with all extrinsic heart nerves divided, they found a very constant pulse-rate and very constant arterial pressure, 20-30 millimetres in cannula placed laterally in the aorta. This very low pressure is, of course, due to the division of the spinal cord, which led to a dilatation of the arterioles all over the body. The blood was nearly stagnant, most of it being accumulated under such circumstances in the abdominal viscera. But little flowed through the lungs, and this small amount was in its transit, no doubt, considerably cooled by the air.

They then varied arterial pressure in three ways: by raising the hinder part of the body of the animal and pressing blood from abdomen to heart, by clamping the aorta or other large vessels near the heart, and by injections of blood into an artery of the animal. All these procedures raised arterial pressure and all quickened the pulse, at least in the earlier stage of the experiment. Let us now analyze these methods; we shall find all of them open to serious objection.

In the first series, pressure was altered by raising and lowering the hinder part of the body. Lifting the hind legs elevates arterial tension and quickens the heart. But even on the face of it, the raised pressure in the aortic system is not the immediate cause of the heart's quicker rate, for the more rapid beat lasts some time after the posterior part of the body is lowered again and aortic pressure has fallen. What, then, is the cause?

It has been proved, mainly by the classical researches of Claude Bernard, that the blood which returns from the abdominal viscera, and especially from the liver, is warmer than that coming from any other part of the body. In the external jugular of a dog the temperature of the blood was found to be 37.7° C. and in the portal vein 39.4° ; that is, nearly two degrees centigrade (more than 3.3° F.) higher; and we may be sure that the blood coming back to the heart through the brachial veins is still lower in temperature than that in the external jugular vein, which, in the dog and rabbit, conveys a very large percentage of the blood that has circulated in the skull cavity far from the skin, and in its course has been warmed rather than cooled.

In v. Bezold's curarized rabbit, with the cervical cord divided, the whole circulation was slow and half stagnant; when he then raised the animal's hind limbs and forced hot abdominal blood in greatly increased quantity to the heart, he not only raised arterial tension, but elevated the temperature of the heart; and such elevation of temperature is abundantly sufficient to account for the quicker pulse. That this is the real explanation is shown, I think, by the fact that the quicker pulse lasts some time after the pressure has returned to its original low level; the heart takes time to cool again.

In other experiments of v. Bezold the chest was opened and the aorta clamped just after the origin of the left subclavian. The original pressure and pulse were 28 millimetres and 184 beats per minute respectively. After the clamping these numbers became 68 and 240. Here again the influence of warmer blood in the coronary system no doubt comes in.

With divided cord most of the blood of the body is stagnant and but little flows through the heart and lungs. With an open chest this little is certainly very greatly cooled in its pulmonary transit by the air forced into the lungs by the apparatus for artificial respiration; given a little blood and much cool air, the blood will reach the left auricle greatly lowered in temperature. When the aorta is clamped, all the blood coming to the heart from the abdomen is sent through the head and neck and forelimbs. This extra quantity more than compensates for the dilatation of the arteries of those parts and a rapid flow is set up through them. Blood warmed by their oxidations now returns to the heart three or four times as fast as it did before from the whole body with unclamped aorta; and this larger amount of blood flowing through the lungs in a given time, while the same amount of air is pumped into those organs, is much less cooled. It reaches the coronary circuit hotter and causes a quicker pulse. After the clamp was removed and the pressure had fallen, v. Bezold found that the pulse kept up to 192 for fifteen seconds.

Finally, v. Bezold and Stezinsky injected into one carotid calf's blood carefully warmed to 38° C. They got rise of pressure and quicker pulse. But, again, temperature changes will explain this. Claude Bernard has shown that while the average normal temperature of the venous blood in a dog is 38° to 40° C., the average temperature of blood in a curarized dog is 35°. No doubt the same thing is true of a rabbit. We have, therefore, an animal with blood at about 35° into whose vessels blood at 38° is injected—obviously enough to influence the rate of heart-beat quite independently of any action of the increased arterial pressure.

It would be tiresome to consider in detail the experiments of other observers on this point. They may all be summed up as open to the same objections as are those of v. Bezold, and with, in most cases, others in addition. I will therefore proceed to give an account of my own work. In it the heart was not only free from the influence of all extrinsic nerve centres, but from all variations in the rate at which venous blood was supplied to it, and from all variations in the composition of this blood, except such as gradually take place as it circulates time and time round and round the heart and lungs, without having fresh material added to it, or having its accumulated wastes carried off by any excretory organ save the lungs. Starting with four or five litres of fresh calf's blood, this can be used for two or three hours before cardiac feebleness shows signs that the blood is so deficient in nutriment or so loaded with wastes as to be no longer fitted to properly nourish the heart.

Moreover, a thermometer placed in the stump of the left subclavian shows accurately the temperature of the blood circulating through the coronary arteries, and therefore that of the blood supplied to the cardiac capillaries.

Whenever the temperature indicated by this thermometer varied more than 0.55° C. (less than a degree Fahrenheit) during an observation, that observation was rejected.

The method of work is as follows: The heart having been isolated and placed in the warm chest, half or three-quarters of an hour are allowed to elapse before taking any observation. This gives time for the cerebro-spinal centres to die and for all things within the warm chest to come to an equable temperature. Then an experiment begins by raising or lowering the opening of the tube connected with the aortic cannula through which the heart pumps blood.

The experiments were conducted in three series: In one the animal was chloroformed while the heart was being isolated; in the second it was placed under the influence of a very full dose of morphia; and in the third it was curarized. In this way was eliminated any specific action which a particular drug might have in throwing out of gear some centre in the heart itself, a centre that might normally be stimulated by raised or lowered arterial pressure. Once the isolation was completed and the defibrinated calf's blood sent through the heart, no drug was any longer given. Both brain and spinal cord being dead, humanity to the animal no longer called for an anæsthetic, and no voluntary or reflex movements could occur to vitiate the experiment.

All being ready, arterial pressure as measured in the carotid was varied between the limits of 40 mm. and 210 mm. of mercury, and tracings taken of it and of the pulse-rate. Then a pause occurred for some five or ten minutes and new tracings were taken in a similar way. The chart on the wall represents graphically a whole experiment. It will be seen that in its course of more than two hours the pulse-rate gradually but on the whole very uniformly falls; but that the pulse-rate is in nowise influenced by intercurrent variations in arterial pressure, even when these are sudden and extreme. There is, however, a point of very high pressure at which the pulse-rate is altered and the character of the beats profoundly modified. This comes in with high venous pressure and great arterial resistance, and is of peculiar interest, for these seem to be exactly the conditions during a spasm of angina pectoris. As yet I have not fully investigated this point, being desirous first of all to gain

some accurate knowledge as to whether the rate of the heart's beat was influenced by variations of arterial pressure such as may be imagined to occur during daily healthy life or in the course of any ordinary physiological experiment. The experiment represented on the chart is only one from a considerable number, all showing that such variations have no influence on the pulse-rate when precautions are taken to insure that nothing but the arterial pressure is varied. It seems clear, therefore, that when the physician finds abnormal arterial tension with abnormally quick or slow pulse, he must look beyond the arterial tension for the direct cause of the modification in the rate of the heart's beat.

The preceding experiments have been concerned only with such variations in the circulatory system as directly affect the left ventricle; a rise or fall of aortic tension determines the amount of energy necessarily expended by that ventricle in forcing open the semilunar valves and driving its contents into the aorta. A different question, but one quite as important, is, what influence, if any, do variations of pressure in the great systemic veins have upon the rate of beat of the heart? If we increase the flow in the great veins the right auricle is more quickly filled, and *a priori* we might well imagine that the pulse-rate would be influenced. Experiment shows, however, that such is not the case. Investigations recently made in my laboratory by Mr. Howell and Mr. Frank Donaldson show that variations in venous pressure greatly affect the work done by the heart, but my own observations show they have no effect on the pulse-rate. v. Bezold and Stezinsky experimented on this subject, raising pressure in the right heart either by injecting blood into the jugular vein, or by clamping the pulmonary artery, and came to essentially the same result. But as above pointed out, such methods of work are open to serious objections; we can never be sure that blood injected from outside has the same temperature as that previously flowing through the right heart; and when the pulmonary artery is clamped, the blood-path to the aorta is blocked or impeded, and the coronary circulation (with the rest of the systemic blood-flow) thus indirectly but seriously interfered with. The results attained by v. Bezold and Stezinsky are as follows: Rise of venous pressure has no direct or definite influence on the pulse-rhythm; it causes a swing to and fro on each side of the previous rate, sometimes quicker, sometimes slower. They conclude by saying that their experiments on this point are too few to be decisive, but tend to show that variations of venous pressure have

no direct influence on the cardiac rhythm. My own experiments fully confirm this. In them arterial pressure was maintained constant by keeping the outflow height of the tube placed in the aorta at the same level. The temperature of the blood sent through the heart was carefully noted by the thermometer in the left subclavian, and only those observations heeded in which this temperature was constant. By raising or lowering the Mariotte's flask connected with the superior vena cava, venous pressure was readily changed. The curves on diagram No. 2 before you represent the results of one such experiment. In essential points all others which I have made agree with it. The rise of venous pressure neither slows nor quickens the pulse.

Next we may proceed to consider the influence of the variations of temperature upon the pulse-rate, a question which, from a clinical point of view, is perhaps of more interest than either of the preceding; variations of temperature being among the most frequent, the most readily observed and the most important symptoms of disease.

It is, I believe, generally accepted that a rise in the temperature of a warm-blooded animal quickens the pulse by direct action on the heart. In the frog we know that such is the case, and it has been assumed for the mammal, though, so far as I know, not experimentally proved hitherto. Indirect proofs of more or less logical stringency have, no doubt, been available—as the slowed pulse of hibernating mammals; the quicker pulse of warm-blooded animals, artificially heated; and in man himself, the rapid pulse of fever. In all of the above cases, however, the heart is in connection with the cerebro-spinal and sympathetic nerve centres, and is also subject to a possible action of products of abnormal tissue change (due to the lowered or raised temperature) carried to it by the veins. In order to be certain that the variations in temperature immediately and directly cause variations in the pulse-rate, it is necessary to observe under conditions when the temperature of the blood flowing through the heart is the only thing varied.

The fathers of medicine have handed down to us the three characteristic symptoms of the most common of pathological conditions, the febrile state, namely, high temperature, dry skin, quick pulse.

The quick pulse implies increased work of the heart, and, doubtless, many a time have each of you, responsible for the life of a patient; gone from a bedside borne down by doubt as to whether the heart could hold out, until the fever should cease, against the enormous extra work

thrown on it by its rapid beat. Exactly how this quick and destructive pulse-rate is produced is a matter of no small interest to mankind; when we know its causation we may hope to learn its remedy. On this point I think that I have been able to add a little to our positive knowledge. Modern physiology has proved that the dry skin of fever is due to nervous disturbance; there is also an increasing body of evidence (see especially the valuable treatise on fever by Dr. H. C. Wood, published by the Smithsonian Institution) that the high temperature of fever is due to a paralysis of heat-regulating cerebral nerve centres. The question now comes in—given as a primary danger in high and continued fever a possible failure of the overworked heart, what is the cause of the quick febrile pulse? Is it like the cessation of perspiration and the high temperature dependent on nervous agencies? Or is it merely a direct result of the increased temperature? On this point, no experiments on a cold-blooded animal can give us any reliable information; those animals have practically no heat-regulating nervous arrangements, and never exhibit true “fever.”

The chart (3) before you shows graphically one experiment in which the temperature of the blood was altered in flowing through the heart of a dog, quite cut off from all extraneous nervous influences, venous and arterial pressures being also kept constant. You see how beautifully parallel the curves of temperature and pulse-rate run. Where one rises the other rises, and where one falls the other does likewise. The pulse-rate is, therefore, most conspicuously dependent upon the temperature of the blood flowing through the coronary arteries, as determined by a thermometer inserted into the subclavian trunk. I confess that the wonderful correspondence of the rise and fall in these temperature and pulse-rate curves gives me peculiar pleasure. The mammalian heart is almost like a thermometer; its pulse-rate rises as uniformly when the temperature of the blood circulating in it rises, and falls as regularly when that temperature falls, as under similar circumstances the mercury rises and falls in the stem of a thermometer.

It will need further experiment to determine finally whether, when the heart is not isolated, any nervous action is exerted on it from outside to quicken its beat during fever. But the fact that (all other conditions being constant) a dog's heart, completely liberated from all possible influence of nerve centres outside of itself, slows its rate of beat from minute to minute as the temperature of the blood sent through the coronary arteries falls, and quickens its beat as the temperature rises, affords very strong presumptive evidence that the quicker pulse of a fevered body is

directly dependent on its higher temperature, and not on any paralysis of the cardio-inhibitory nerve centres, or any excitation of cardio-accelerator centres. The change in pulse-rate is apparently no indirect thing due to nervous derangements outside the heart, but the immediate consequence of the warmer blood circulating in the capillaries of that organ. If this be so, speaking as an outsider, and feeling that I am going beyond my province in this assembly of men whose lives are devoted to the treatment of disease, I feel nevertheless impelled to point out the bearing of the fact in those cases of fever in which death is imminent from failure of the overworked heart. By putting a patient in a bath whose temperature is gradually and carefully lowered, it seems probable that the heart's beat can be slowed as the body is cooled, the extra strain on it diminished, and threatened death possibly averted.

There still remain in this connection two points of peculiar interest. What is the highest temperature at which the heart can live, and what is the lowest? Also, what is the temperature of best work? On none of these subjects have I yet had time to make a complete series of observations; but I can state that the dog's heart will still beat regularly, though slowly, at 26° C., and regularly, but rapidly and feebly, at 41° C.

I have already detained you longer than I intended, but I feel that I must say a few words more. When I laid before the Faculty last year a statement of the method devised by me for isolating the heart of the warm-blooded animal and studying its physiology, it seemed to me a very simple matter to take the three factors, venous pressure, arterial pressure, and temperature, and, keeping any two of them constant, vary the third, so finding out its influence pure and simple. In practice, however, the matter proved by no means easy, and it was only by degrees that the more perfect manner of experimenting which I have to-day described was arrived at. It is my duty as well as my pleasure in announcing some of the results to also publicly acknowledge the assistance which I have received from my pupils in completing the mechanical arrangements and in carrying out the various experiments. From time to time as new difficulties arose and had to be met in controlling arterial pressure, or venous pressure or temperature, I have received so much valuable assistance and so many hints as to modifying the apparatus and the method, that I now hardly know what part of the perfected method is mine, what that of one or another of my pupils and assistants. The method as it now stands is the Baltimore method, and not that of any one individual, and as such, in so far as it has any value, should go forth to the world.

III.

OBSERVATIONS ON THE DIRECT INFLUENCE OF VARIATIONS OF ARTERIAL PRESSURE UPON THE RATE OF BEAT OF THE MAMMALIAN HEART.

With Plate 2.

[*Studies from the Biological Laboratory of the Johns Hopkins University,*
Vol. II, p. 213, 1882.]

The earliest observations on this subject, so far as I know, were made by Marey (*Recherches sur le pòuls au moyen d'un nouvel appareil enrégistreur. Memoires de la Société de la Biologie, 1859*); but as the extrinsic cardiac nerves were not divided in his experiments, and a rise of blood pressure is now known to stimulate the medullary cardio-inhibitory and accelerator nerve centres, the results obtained by him give really no information as to the direct influence of increased aortic tension upon the rate of the heart's beat. Since then others have experimented, previously dividing the extrinsic cardiac nerves, Ludwig and Thiry in 1864 (*Sitzb. d. Akad. d. Wissensch. zu Wien*) leading the way, but the general result is that the matter has been left in a highly unsatisfactory state. Some find that variations of arterial pressure have no effect on a heart whose venous connections with other parts of the body have been severed; others that arterial pressure and pulse rate rise and fall together; others that the pulse quickens when arterial tension is lowered and *vice versa*. Finally, Tschirjew (*Arch. f. Anat. u. Physiologie, Jahrgang 1877, p. 116*), the latest writer on the subject, finds all of the above effects in different cases: as the result of an extensive series of experiments he comes to the conclusion that after section of all the extrinsic heart nerve paths, "any considerable and rapid elevation of blood pressure may directly stimulate either the inhibitory apparatus in the heart, or its motor ganglia, and the pulse rate accordingly be increased or diminished, or in more rare cases remain unaltered." Such contradictory results obtained by a number of competent workers lead naturally to the suspicion that some error is involved in the methods of experiment employed; the nature of this error is not, I think, far to seek. The methods used to vary arterial pressure have been such as cause variations also in several other condi-

tions which either are known to influence the heart, or may possibly do so; nevertheless all these secondary actions have been unheeded: their relative prominence in any given experiment has not been noted, and any change in the pulse rate has been ascribed solely to the changed arterial pressure. Under such circumstances it need cause no surprise that very inconsistent results should be obtained.

The higher aortic pressure is, the more force must be expended by the left ventricle in forcing open the semilunar valves; that is to say, the higher will be intraventricular systolic pressure. It is this influence only of increased aortic pressure which should be meant when its direct action upon the cardiac rhythm is spoken of; and to get pure results all other consequences of increased arterial tension which may influence the heart's rate of beat must be eliminated. This, however, has not been the case in any series of experiments with which I am acquainted.

Arterial pressure has commonly been increased by clamping the descending aorta, either in the thorax or abdomen. When this is done, however, we alter several other things in addition to arterial pressure—

(1.) The amount of blood returned to the right auricle in a given time is almost certainly altered, and therefore the rate of filling of the heart during diastole.

(2.) The pressure under which venous blood enters the right auricle is probably changed, and therefore intracardiac pressure at the end of the diastole.

(3.) The temperature of the blood returned to the heart by the systemic veins and, as a consequence, of the heart itself, is altered. The blood returned to the right auricle by the inferior cava is known to be warmer than that returned by the superior cava, which has not flowed through the hot abdominal organs. When the aorta is clamped the heart gets only the cooler superior cava blood, as the capillary tracts tributary to the inferior cava are no longer supplied with blood.

(4.) It is known that very slight chemical changes in the blood profoundly influence the heart's beat. To quote no other instance, Gaule has shown that the heart of a frog previously kept in the cold and exhibiting deficient functional power may be restored to full vigor by circulating through it the extract of the heart of a frog kept previously at a higher temperature. Blood in its flow through the abdominal organs experiences important chemical changes entirely differing from any undergone in other regions of the body. If, therefore, we circulate blood through head, neck and fore-limbs only, and return it again and again to the heart

without exposing it to the action of kidneys, spleen and liver, we very soon have a liquid to deal with which is essentially different from that which flowed through the heart before the aorta was ligated.

Of course when the arterial pressure is lowered by opening the previously clamped aorta all of the above possible disturbing actions occur in the opposite direction.

Another method which has been employed to raise arterial pressure is to inject blood from another animal into the carotid of the animal experimented upon. This also involves several possible sources of error. (1) Venous inflow during cardiac diastole is almost certainly changed. (2) Venous pressure and, therefore, intracardiac diastolic pressure are probably altered. (3) The injected blood may differ chemically from that already in the vessels, and directly act upon the heart. (4) Unless extreme care be taken the temperature of the injected blood will be less or greater than that of the already circulating blood, and will alter the temperature and, therefore, the rhythm of the heart. To the above objections it may be added that only slight increase of arterial pressure can be brought about in this way; as is proved by Worm Muller's experiments (*Arbeiten aus d. physiol. Anstalt zu Leipzig, 1873*).

When blood pressure is lowered by bleeding, diastolic inflow and pressure are altered as well as arterial pressure; and also probably the chemical metabolisms experienced by the blood in its flow through different organs.

As some one, at least, of the above secondary influences has been present in all previous experiments as to the influence of variations of arterial pressure upon the pulse rate, it is clear that none of these experiments, interesting and important as their results are in many cases, are really capable of affording an answer to the question in hand, viz. what is the influence, if any, pure and simple, of increased aortic pressure (*i. e.* of increased systolic pressure within the left ventricle) on the pulse rate. It is, therefore, not necessary to consider in detail the experiments of previous writers. All are vitiated more or less by secondary changes which have occurred along with the variations of arterial pressure; and the number of these possible complications, and their varying degree in different experiments, affords a sufficient explanation of the contradictory results obtained.

As regards the frog's heart there is more agreement between observers, and the experimental conditions have usually been more

satisfactory. Usually the auricle is supplied steadily with liquid of constant composition and at constant pressure from a Mariotte's flask; but even here, so far as I know, the arterial cannula has always been inserted into the ventricle and, therefore, beyond the semilunar valves. As a necessary consequence of this, not only systolic ventricular pressure (which normally is the thing changed by varied arterial pressure), but also diastolic intraventricular pressure has been varied. I accordingly suggested to two of my pupils that they should undertake a fresh examination of this question by better methods, on the hearts of frogs and chelonia. Some results of their work will be found on subsequent pages of the present number of this Journal.

The question involved is clearly one of great importance. In almost every experiment relating to cardiac physiology arterial pressure is altered; and it is essential to know exactly the direct influence of this factor on the heart, before further conclusions can be legitimately arrived at. I have, therefore, lately carried out a large number of experiments as to the direct influence of variations of arterial pressure upon the pulse, making use of the dog's heart completely isolated physiologically from every other organ but the lungs: the method of isolation, which essentially consists in closing the whole systemic circulation except that through the coronary vessels of the heart itself, was described by me in the last number of this Journal (Vol. II, No. 1, p. 119); as the apparatus has since been modified only in some points of detail, I here reproduce, as Plate XV [Plate 2 of this volume], the figure used in illustrating the previous paper, in order to assist in the description of my more recent experiments.

The right and left carotid arteries, *o* and *r*, have cannulas placed in them, the right subclavian, *w*, is ligatured, and a cannula is put in the left subclavian, *m*. Then the aorta is ligated immediately beyond the origin of the left subclavian: the vena cava inferior and the azygos vein are tied, and a cannula put in the superior cava. Fresh defibrinated strained and warmed blood is now run in by the superior cava; at the same time the cannula on the right carotid is opened and blood drawn from it until there is reason to believe that all the blood originally in the heart and lungs of the animal has been washed out; the carotid is then again clamped, and the superior cava a few seconds later, when the heart and lungs have been tolerably well filled with blood. The animal is then transferred to the warm moist chamber *K*, the cannula of the superior cava is connected with one of the Mariotte's flasks, 27 or 28, from which a nutrient liquid is sent into the heart under a uniform pressure,

which in the experiments described below was that exerted by a column of blood 10 centimetres in height. The left carotid, *o*, is connected with the outflow tube, 21, and the cannula in the subclavian with a mercurial manometer, 26, the pen of which writes on the paper of a kymographion in the usual manner. As soon as one Mariotte's flask is empty its connection with the heart is shut off, and that of the other (which has been meanwhile closed) is freed by opening the proper one of the clamps, 1 or 2, and closing the other. The nutrient liquids employed in the experiments below described were (1) fresh defibrinated strained dog's blood; (2) the same diluted with an equal bulk of 0.5 per cent. solution of sodium chloride in distilled water. I may here state that in other cases I have used with success (3) defibrinated dog's blood with one-third its bulk of 0.7 per cent. sodium chloride solution; and (4) defibrinated calf's blood.

Under these conditions almost all of the ordinary collateral results of increased or lowered arterial pressure can be eliminated. By closing more or less completely the stop-cock, 22, arterial pressure can be raised; by opening the stop-cock wider it can be diminished. Meanwhile, rate of supply to the right auricle, the temperature of the liquid sent into it, and the composition of this liquid are unvaried; all these disturbing elements are thus got rid of. I have said above that "almost" all secondary effects can be eliminated; the *almost* is due to the varied coronary circulation; when aortic pressure is high this must be greater than when that pressure is low; so far I see no method of eliminating this possible source of error; but in recent years much evidence has been accumulated to show that if the flow of blood through an organ is sufficient to nourish it (*i. e.* does not fall below the starvation limit), and is under a lower pressure than such as ruptures the vessels or otherwise mechanically impedes the action of the organ, there is much reason to believe that variations in blood supply have no immediate influence on its functional activity. The experiments detailed below give further support to this view: as will be seen, variations of arterial pressure ranging between 25 and 150 mm. of mercury have no influence whatever upon the heart's rhythm, although considerably more blood must flow through the coronary system under the higher than under the lower pressure.

In the experiments described below, the heart was always left in the warm chamber at least half an hour before observations were made, and longer if the thermometer did not show that the temperature was then uniform and had been for some five or ten minutes. The animals during the isolation of the heart were sometimes placed under the influence of morphia, sometimes of curari, and sometimes of chloroform; these

various agents were used to eliminate chances of error due to the possible toxic action of any one of them on a regulatory mechanism in the heart, though when fresh unpoisoned defibrinated blood is run for hours through the heart after its isolation, there can be little doubt that any poison absorbed by the organ during the preliminary observation is thoroughly washed out. The animals used were small dogs, weighing from 6 to 7.5 kilos. Uniform artificial respiration was kept up by means of a small water engine.

When temperature had become constant, the connection between a full Mariotte's flask (containing about 700 cc. of liquid) and the heart was opened. A minute or two was allowed to elapse, to get a steady inflow current; then arterial pressure was raised by partially closing the stop-cock, 22, or lowered by opening it wider. Tracings were taken for from two to six minutes with arterial pressures varied in this way; then the observation ceased. Meanwhile the other Mariotte's flask was filled; and after some minutes another observation was made while it was connected with the heart; and so on, so often as seemed desirable. In all cases the experiment came to an end long before the heart showed signs of abnormal or irregular action; indeed in most instances it was subsequently used for preliminary observations on the influence of other conditions, as varied venous pressure or varied temperature on the pulse rate.

The results arrived at may be summed up as follows:

1. *When the pressure under which blood of uniform temperature and composition is steadily supplied to the right auricle does not exceed that due to a column of blood ten centimetres in height, no variation of arterial pressure which can be brought about by opening or closing more or less completely the outflow stop-cock, has any influence whatever on the rhythm of a heart isolated from all other organs of the body except the lungs, provided arterial pressure be not kept at a very low level for a considerable time. In other words, within very wide limits, changes in arterial pressure have no influence whatever upon the pulse rate.*

2. *If the outflow stop-cock be widely opened and arterial pressure lowered to less than twenty millimetres of mercury, this has no direct influence on the pulse rate; but it has probably an indirect influence. For a minute or more the heart beats recur at the same intervals, but after that time, if the lower pressure be still maintained, the pulse sometimes becomes slower, probably from deficient nutrition of the heart dependent on insufficient flow through the coronary vessels.*

3. *If the pressure at which venous blood enters the right auricle be considerable (due to a column of blood forty centimetres in height), and if*

simultaneously the arterial exit be greatly narrowed by closing the outflow stop-cock, then arterial pressure at first rises greatly without any alteration in the pulse rate; but ultimately attains a very high level at which the cardiac rhythm becomes extremely irregular. Beats occur which somewhat resemble those produced by feeble pneumogastric stimulation. If the arterial resistance be now diminished, markedly dicrotic beats occur for some twenty or thirty seconds, until arterial pressure again falls to a normal level, when the original pulse rate is resumed. The conditions when the irregular beats are observed are clearly pathological; a filling of the heart under a pressure in the vena cavae equal to forty centimetres of blood (twenty-nine millimetres of mercury) probably never occurs normally combined with great arterial resistance.

In the present article I shall confine myself to what may be called normal variations of arterial pressure, that is to say, for small dogs, variations between 25 and 160 millimetres of mercury. The result under the above heading 2 is undoubtedly abnormal, and due to commencing death of the heart; and the results indicated under No. 3 are probably due either to the reception by the left ventricle in each diastole of more blood than, under the resistance opposed to it, it can pump out in one systole, or to a direct stimulation of inhibitory mechanisms in the heart by the pathological pressure within the ventricle. This irregular beat with very great arterial resistance has been noted by Heidenhain, and I may here state that Knoll's opinion that it really means not a slowed heart beat, but a quick irregular beat which the manometer does not properly record, is incorrect; direct observation of the exposed heart is conclusive as to the fact that the beats are not quick and irregular, but really slow, and frequently dicrotic.

On the results numbered 2 and 3 above I desire to make further observations before publishing detailed conclusions. Hitherto, so soon as I have observed indications of them I have at once raised or lowered arterial pressure so as to prevent death or injury to the heart. As regards point 1, the three tables below speak for themselves. They are selected from a dozen experiments which are perfectly concordant, and they have been so selected that a different drug was given to the dog during the preliminary operation of isolating the heart in each case. The venous inflow was always so proportioned to the resistance to arterial outflow that pressure in the subclavian during the intervals between any two observations was kept at a point from which arterial pressure could be considerably raised without the variation passing beyond a physio-

logical limit; but at the same time, a pressure sufficient to keep the heart in a functional condition for a long time.

Venous pressure in all the experiments recorded below was that due to a column of nutrient liquid (defibrinated dog's blood, or the same diluted with an equal volume of sodium chloride solution) ten centimetres in height, or very near that; it is not well practicable to measure exactly in every experiment the difference in level between the cannula in the superior cava and the lower end of the tube for the entry of air into the Mariotte's flask; but errors of a few millimetres in this regard are of no importance: so long as the pressure is constant during an observation a knowledge of its absolute amount within 5 or 6 millimetres of blood is of no consequence.

The tables are constructed as follows: Temperature in the moist warm chamber having become constant, the kymographion was started and tracings taken for from two to seven minutes. During this time the stop-cock, 22, was opened wider, or more closed, or opened and then closed, or *vice versa*, and consequently arterial pressure was altered. A number of such observations having been made, the tables were constructed from the tracings obtained: suppose the time to be 2 h. 20' 10", then arterial pressure is measured at that time and at 2 h. 20' 20". Half the sum of these is taken as the mean pressure during the intervening ten seconds. The pulse rate is counted for this ten seconds, multiplied by 6, and the product given as the rate of heart beat per minute, with the mean arterial pressure obtained as above. So far as absolute results are concerned, it is seen that the mean arterial pressure arrived at in this way is open to some error, and had changes in it been accompanied by changes in the pulse rate, more accurate methods of arriving at the true mean arterial pressure during each ten seconds would have to be employed. But as very great variations of mean arterial pressure were used and as the experiments show that none of them, within the limits described above as physiological, cause any change in the rate of the heart's beat, it is clearly unnecessary to resort to planimetry or other troublesome methods so as to avoid possible errors of a few millimetres in the measurements. When gross variations of arterial pressure from 30 to 150 mm. of mercury cause no change, it is not worth while to spend time in endeavoring to exclude possible errors of ten or even fifteen millimetres of mercury pressure; and the possible limits of error in my measurements never reached the less of those quantities. When the lungs are kept well extended and the artificial respiration apparatus works with tolerably slow powerful blasts, marked respiratory waves are

seen on the tracings of arterial pressure, unless this fall to 50 millimetres of mercury or thereabouts, when they disappear. As these rhythmic rises and falls of arterial pressure render it more difficult to correctly arrive at the mean pressure, I have usually eliminated them by arranging my water engine so as to work with rapid short strokes; then respiratory variations of arterial pressure entirely disappear from the manometer tracings.

In the experiments recorded below, the heart had been physiologically isolated from all other organs but the lungs for some considerable time before the recorded observations were made; the muscles of the body in general were often already in marked rigor before the first observation was made and always long before the last. When the words "no record" appear in the details of an observation, some one or more of the pens was not writing, so that either time, pressure, or pulse rate, could not be determined. The temperature given is that of the warm chest in which the animal lay.

EXPERIMENT A.

October 13, 1881. Small dog, narcotised with morphia during the operation of isolating the heart. Nutrient liquid 1,400 cub. cent. of defibrinated dog's blood drawn from two other animals. Arterial pressure measured in left subclavian. Heart isolated and animal put in warm chamber at 4 h. 10' P. M.

Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.	Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.
I	4 h. 44' 00"	37°	137	147	II	4 h. 58' 50"	37°	133	147
	" 10		134	147		4 h. 59' 00"		134	149
	" 20		131	146		" 10		139	147
	" 30		132	147		" 20		143	150
	" 40		116	147		" 30		144	150
	" 50		89	147		" 40		142	149
	4 h. 45' 00"		74	147		" 50		138	149
	" 10		83	150		5 h. 00' 00"		136	148
	" 20		109	147		" 10		129	150
	" 30		124	147		" 20		104	150
	" 40		134	150		" 30		82	150
	4 h. 46' 00"		149	150		" 40		87	150
	" 10		142	149		" 50		117	151
	" 20		120	147		5 h. 01' 00"		123	148
	" 30		98	147		" 10		129	151
	" 40		83	150		" 20		133	150
	" 50		99	147		" 30		130	150
						" 40		110	150
						" 50		90	151

EXPERIMENT A.—*Continued.*

Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.	Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.
III	5 h. 17' 00"	37°	112	150	IV	5 h. 29' 40"	37°	80	150
	" 10		119	150		" 50		81	153
	" 20		102	150		5 h. 30' 00"		80	156
	" 30		80	150		" 10		82	150
	" 40		87	No record		" 20		93	156
	" 50		100	150 (?)		" 30		104	153
	5 h. 18' 00"		108	No record		" 40		110	153
	" 10		114	150		" 50		112	156
	" 20		119	150		5 h. 31' 00"		111	153
	" 30		125	No record		" 10		112	150
	" 40		126	151		" 20		99	150
	" 50		112	150		" 30		80	156
	5 h. 19' 00"		89	150		" 40		82	156
						" 50		93	153
						5 h. 32' 00"		102	156
						" 10		100	156
						" 20		86	156
						" 30		85	150
						" 40		97	156
						" 50		102	152

In observation I, arterial pressure varied between 74 and 149 millimetres of mercury (101 per cent.) and the pulse rate between 147 and 150 per minute (2 per cent.). In observation II, arterial pressure varied between 82 and 144 millimetres of mercury (75.6 per cent.) and the pulse rate between 147 and 151 per minute (2 per cent.). In observation III, arterial pressure varied between 80 and 126 millimetres of mercury (57.5 per cent.) and the pulse rate between 150 and 151 per minute (0.66 per cent.). In observation IV, arterial pressure varied between 80 and 112 millimetres of mercury (40 per cent.) and the pulse rate between 150 and 156 per minute (4 per cent.).

EXPERIMENT B.

October 15, 1881. Small dog, curarised during the preliminary operation. Nutrient liquid, 1,350 cub. cent. of defibrinated dog's blood taken from two other animals. Arterial pressure measured in left subclavian. Operation completed and animal placed in warm chest at 1 h. 50' P. M.

EXPERIMENT B.

Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.	Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.
I	2 h. 17' 50"	34.5°	53.5	120	IV	3 h. 29' 10"	35°	91	102
	2 h. 18' 00"		78.5	120		" 20		73	102
	" 10		116.5	120		" 30		59	102
	" 20		No record	No record		" 40		43	102
	" 30		No record	No record		" 50		44	102
	" 40		86	120	V	3 h. 31' 20"	35°	63	98
	" 50		75	120		" 30		81	102
	2 h. 19' 00"		69	120		" 40		98	98
	" 10		66	120		" 50		110	99
	" 20		80.5	122		3 h. 32' 00"		119	100
	" 30		102.5	122		" 10		No record	No record
	" 40		114	121		" 20		No record	No record
	" 50		121	120		" 30		No record	No record
II	2 h. 44' 00"	35°	53	117		" 40		No record	No record
	" 10		57.5	117		" 50		127	101
	" 20		84	117		3 h. 33' 00"		106	102
	" 30		117	123		" 10		70	102
	" 40		136	114		" 20		54	101
	" 50		145	118.5		" 30		47	99
	2 h. 45' 00"		104	114		" 40		55	100.5
	" 10		67	118.5		" 50		72	103
	" 20		51	114		3 h. 34' 00"		89	102
	" 30		49	117		" 10		104.5	102
	" 40		49	117		" 20		112.5	101.5
	" 50		35	117		" 30		122	103
	2 h. 46' 00"		27	114		" 40		130	102
	" 10		25	117		" 50		131	103
	" 20		23	117		3 h. 35' 00"		111	104
	" 30		22	114		" 10		80	102
	" 40		22.5	114		" 20		65	100
	" 50		22.5	113		" 30		40	102
	2 h. 47' 00"		21	111		" 40		51	102
III	" 10		20	111		" 50		56	102
	" 20		25	114.5	VI	3 h. 40' 55"	35°	50.5	102
	" 30		45	110		3 h. 41' 05"		58.5	101
	2 h. 54' 50"	35°	148	108		" 15		64	102
	2 h. 55' 00"		116	108		" 25		64	102
	" 10		78	112		" 35		66	102
	" 20		56	108		" 45		80	102
	" 30		43	109.5		" 55		100	102
	" 40		38	108		3 h. 42' 05"		114	102
	" 50		41	108		" 15		101	102
	2 h. 56' 00"		51	108		" 25		71	102
	" 10		57	108		" 35		61	102
IV	" 20		89	112		" 45		75.5	103
	" 30		131	111		" 55		98.5	102
	" 40		143	110		3 h. 43' 05"		112	104
	3 h. 27' 40"	35°	72.5	99		" 15		102	103
	" 50		87.5	102		" 25		74	102
	3 h. 28' 00"		99.5	100		" 35		56	101
	" 10		117.5	99		" 45		45	100
	" 20		128	102		" 55		33	102
	" 30		140	103		3 h. 44' 05"		25	102
	" 40		No record	No record		" 15		23	102
	" 50		No record	No record		" 25		22	104
	3 h. 29' 00"		No record	No record		" 35		18.5	102
						" 45		17.5	103

In observation I of the above experiment arterial pressure varied between 53.5 and 116.5 millimetres of mercury (117 per cent.) and the pulse between 120 and 122 per minute (1.6 per cent.). In observation II, arterial pressure varies between 20 and 145 millimetres of mercury (625 per cent.) and the pulse rate between 110 and 118.5 per minute (nearly 8 per cent.); this it will be seen on closer examination is one of the cases above referred to, which lead to the suspicion that a continued arterial pressure (as measured in the subclavian) of less than 30 millimetres of mercury is insufficient to nourish the heart and leads to a slowing of its beat. Arterial pressure was kept below this limit for nearly one and a half minutes, and the pulse rate fell from 117 to 110. In observation III, arterial pressure varies between 38 and 148 millimetres of mercury (290 per cent.) and the pulse rate between 108 and 112 per minute (3.6 per cent.). In observation IV, arterial pressure varies between 43 and 140 millimetres of mercury (225.5 per cent.) and the pulse rate between 99 and 103 per minute (4 per cent.). In observation V, arterial pressure varies between 40 and 111 millimetres of mercury (177.5 per cent.) and the pulse rate between 100 and 104 per minute (4 per cent.). In observation VI, arterial pressure varies between 17.5 and 114 millimetres of mercury (551.5 per cent.) and the pulse rate per minute between 100 and 104 (4 per cent.).

EXPERIMENT C.

October 26, 1881. Small dog, anæsthetised by chloroform during the operation of isolating the heart. Nutrient liquid, 800 cc. of defibrinated dog's blood mixed with 800 cc. of 0.5 per cent. solution of pure sodium chloride in distilled water. Heart isolated and animal placed in warm chest at 12 h. 50' P. M. When the series of observations detailed below was concluded the heart was still in good condition and was used for two hours for other experiments.

EXPERIMENT C.

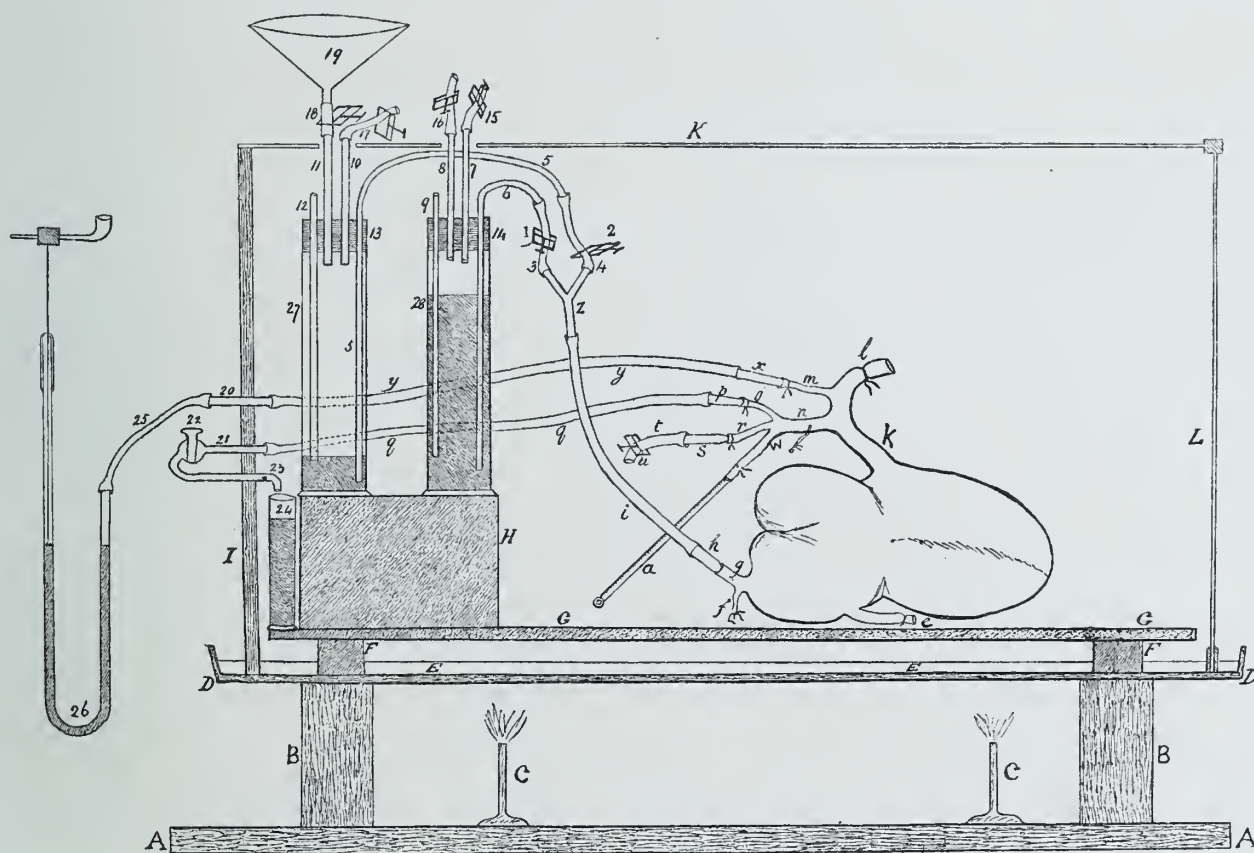
Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.	Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.
I	1 h. 23' 10"	37°	29	102	II	1 h. 38' 50"	37°	25	100.5
	" 20		30	103		1 h. 39' 00"		24	100.5
	" 30		30	102		" 10		24	102
	" 40		30	102		" 20		26	102
	" 50		33	103		" 30		27	102
	1 h. 24' 00"		40	102		" 40		26	100.5
	" 10		46	103		" 50		28	100.5
	" 20		51	102	III	1 h. 57' 30"	37°	28	96
	" 30		59	102		" 40		38	94
	" 40		63	103		" 50		24.5	97
	" 50		56	101		1 h. 58' 00"		29.5	95
	1 h. 25' 00"		46	102		" 10		33	96
	" 10		40	102		" 20		25	96
	" 20		35	103.5		" 30		14.5	99
	" 30		42	102		" 40		12	95
	" 40		58	103		" 50		14.5	96
	" 50		70	102		1 h. 59' 00"		20	96
	1 h. 26' 00"		79	105		" 10		24.5	96
	" 10		80	104.5		" 20		29	96
	" 20		No record	No record		" 30		34	98
	" 30		40	105		" 40		37.5	99
	" 40		36	105		" 50		30	96
	" 50		26	105	IV	2 h. 02' 10"	37°	51	100
II	1 h. 33' 20"	37°	40	100		" 20		54	100.5
	" 30		42	101		" 30		64	100.5
	" 40		43	102		" 40		76	102
	" 50		44	102		" 50		87	102
	1 h. 34' 00"		37	102		2 h. 03' 00"		94	102
	" 10		30	102		" 10		89	103
	" 20		25	102		" 20		56	105
	" 30		25	101		" 30		30	102
	" 40		28	101		" 40		37	102
	" 50		29	101		" 50		54	105
	1 h. 35' 00"		28	102		2 h. 04' 00"		70	108
	" 10		27	102		" 10		81	104
	" 20		29	101		" 20		89	104
	" 30		39	100.5		" 30		95	106
	" 40		52	102		" 40		99	105
	" 50		63	102		" 50		106	105
	1 h. 36' 00"		72	102		2 h. 05' 00"		81	105
	" 10		56	102		" 10		39	105
	" 20		32	102		" 20		21	105
	" 30		29	101.75		" 30		24	104
	" 40		41	101		" 40		35	105
	" 50		58	102		" 50		50	108
	1 h. 37' 00"		68	102		2 h. 06' 00"		64	105
	" 10		78	103		" 10		77	108
	" 20		87	103		" 20		88	109
	" 30		93	105		" 30		81	110
	" 40		98	102		" 40		48	108
	" 50		101	102		" 50		23	108
	1 h. 38' 00"		103	102		2 h. 07' 00"		27	108
	" 10		88	102		" 10		42	107
	" 20		53	102		" 20		59	109
	" 30		29	102		" 30		73	110
	" 40		25	101					

EXPERIMENT C.—*Continued.*

Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.	Observation.	Time.	Temperature in degrees C.	Arterial Pressure in mm. of Mercury.	Pulse Rate per Minute.
IV	2 h. 07' 40"	37°	83	111	V	2 h. 20' 00"	37°	77	105
	" 50		77	109		" 10		53	105
	2 h. 08' 00"		No record	No record		" 20		29	105
	" 10		19	109		" 30		23	105
	" 20		18	109		" 40		22	105
	" 30		19	109		" 50		24	105
V	2 h. 17' 20"	37°	25	105		2 h. 21' 00"		30	105
	" 30		26	108		" 10		39	105
	" 40		29	105		" 20		45	106.5
	" 50		33	105		" 30		53	105
	2 h. 18' 00"		40	106		" 40		61	106.5
	" 10		49	106		" 50		66	106.5
	" 20		53	106		2 h. 22' 00"		71	106.5
	" 30		57	106.5		" 10		No record	No record
	" 40		63	106.5		" 20		No record	No record
	" 50		68	106.5		" 30		76	106.5
	2 h. 19' 00"		71	106.5		" 40		69	106.5
	" 10		72	106		" 50		46	106.5
	" 20		73	106.5		2 h. 23' 00"		26	106.5
	" 30		76	108		" 10		22	106.5
	" 40		77	106		" 20		21	106.5
	" 50		78	107		" 30		20	106.5

In observation I of the above experiment, arterial pressure varied between 26 and 80 millimetres of mercury (207 per cent.) and the pulse between 101 and 105 per minute (4 per cent.). In observation II, arterial pressure varied between 24 and 103 millimetres of mercury (329 per cent.) and the pulse rate between 100 and 105 per minute (5 per cent.). In observation III, arterial pressure varied from 12 to 38 millimetres of mercury (216.5 per cent.) and the pulse rate from 94 to 99 per minute (5 per cent.). In observation IV, arterial pressure varied between 18 and 106 millimetres of mercury (863 per cent.) and the pulse rate between 100 and 111 per minute (11 per cent.). In observation V, arterial pressure varied between 20 and 78 millimetres of mercury (290 per cent.) and the pulse rate between 105 and 108 per minute (less than 3 per cent.).

A critical examination of the preceding tables will, I think, show conclusively that variations in arterial pressure within the limits indicated in them have no influence on the pulse rate of the isolated dog's heart. In the great majority of cases the variations in the pulse rate fall clearly within the limits of error of the experiment (2-3 per cent.), while arterial pressure is greatly varied. Eliminating the obviously exceptional





observations II, Expt. B, and IV, Expt. C, the average variation of arterial pressure in an observation was 204 per cent., and the average variation in the pulse rate 3.3 per cent.

That the possible sources of error will readily account for the pulse changes in most cases is clear—when it is remembered (1) that a mistake of one-sixth of a beat in counting out the pulse in any period of ten seconds appears in the tables as an error of one beat per minute; (2) that the temperature of the air pumped through the lungs and influencing the temperature of the blood was often unavoidably altered during the course of an observation, as the doors of my present experiment room, which unfortunately is somewhat of a thoroughfare, were opened by passers-by from time to time. The latter influence is of great importance, as experiments which I hope shortly to publish, have proved that the dog's heart is, so far as its rhythm is concerned, extremely sensitive to slight variations in temperature.

Whatever the cause of the slight pulse-rate changes observed may be, it is at least clear that they are not dependent on varied aortic pressure, for there is no possible relationship, direct or inverse, to be detected between the two, when the whole series of observations is examined. In most cases great variations of arterial pressure are seen to occur without any change in the pulse rate, and then, a little later in the same observation perhaps, the pulse alters two or three beats a minute without any considerable simultaneous change in arterial pressure.

If the relationship between pulse rate and arterial pressure were invariable, even 3.3 per cent. of variation in the pulse per minute might clearly be significant; but as there is no such constant relationship, and the known sources of error fully account for such pulse-rate variations as were observed, they obviously mean nothing in this connection: and we may safely conclude that *within the limits of aortic pressure indicated by pressures varying between 25 and 140 millimetres of mercury in the subclavian, no change of pressure has any direct action upon the rate of beat of the isolated heart of the dog.*

Before concluding, it is my duty and pleasure to acknowledge the willing and skillful assistance in the execution of my experiments rendered to me by Mr. H. H. Donaldson and Mr. Mactier Warfield, who not only undertook the tedious task of getting ready the apparatus for each experiment, but gave me most important help in carrying it through.

IV.

THE DIRECT INFLUENCE OF GRADUAL VARIATIONS OF TEMPERATURE UPON THE RATE OF BEAT OF THE DOG'S HEART.

With Plates 3 and 4.

[*Croonian Lecture: Philosophical Transactions of the Royal Society of London, Vol. 174, p. 663, 1883. An abstract of this paper appeared in the Proceedings of the Royal Society, London, Vol. 34, p. 444, 1883, and in the Studies from the Biological Laboratory of the Johns Hopkins University, Vol. II, 495, 1883.*]

INTRODUCTION.

In the year 1881 I briefly described (1) a method of experimenting by which the heart and lungs of a dog or cat could be completely isolated physiologically from the remainder of the body of the animal, and kept alive some hours for study in an apparently normal condition, the heart beating regularly and maintaining a good arterial pressure. Since then I have been at work investigating the influence of various conditions upon the pulse rate of dogs' hearts so isolated; while under my supervision several of my pupils have been engaged in studying the work done in a unit of time by such hearts under different external conditions.

As regards the effects of variations of arterial pressure upon the pulse rate of the isolated dog's heart, my results have already been published (2); and detailed observations as to the influence of variations in venous pressure will shortly be printed. But in so far as the influence of temperature variations upon the cardiac rhythm is concerned, only a brief preliminary announcement (3) has been made. In the present paper I propose to give a full account of my experiments upon this subject, which is one that, apart from and in addition to its purely physiological interest, has considerable practical importance in connection with inquiries as to the immediate cause of the quick pulse so constantly found in warm-blooded animals suffering from fever.

Almost all that we have hitherto known concerning the direct influence of temperature changes upon the cardiac rhythm is derived from experiments made upon cold-blooded animals, especially frogs. As regards

these animals all observers are agreed that as the temperature of the heart is gradually raised from near zero to about 40° C., its beat is quickened. It is clear, however, that we can only argue with much reserve from the heart of the frog to that of the mammal when the direct effect of temperature variations is concerned. The frog can hardly be said to have any normal temperature, and has but slightly developed temperature-regulating physiological mechanisms; its healthy temperature varies from a very low point in midwinter to 32° C. or above on a Baltimore summer day. The mammal, on the contrary, is constructed to maintain a definite normal temperature, which does not vary beyond very narrow limits; a departure of even a couple of degrees from this normal is always the sign or the cause of pathological processes. We find the mammalia, accordingly, provided with highly complex temperature-regulating mechanisms, in possessing which they differ very sharply from the amphibia. While it might therefore be expected *a priori* that the frog's heart is so constructed as to work better at those warm temperatures at which the general neuro-muscular apparatus of the animal is most active, and the calls upon the organs of nutrition greatest, the discovery that such is actually the case and that the warmed hearts of frogs beat quicker than cold, does not justify us in forthwith concluding that the mammalian heart, placed in and adapted to the needs of an animal with only one healthy temperature, would behave in like manner. This doubt concerning the validity when extended to warm-blooded animals of arguments based on experiments made with the hearts of frogs is increased when we call to mind the fact that an elevation, within physiological limits, of the temperature of the medium to which a cold-blooded animal is exposed increases its tissue metamorphoses, as evidenced by a greater excretion of carbon dioxide, while exactly the reverse is the case in respect to the mammal. Recalling the wonderful physiological adaptation of the organs of animals to the conditions under which they live, we might almost expect that increased temperature (not reaching pathological limits) of the blood carried to it would lead to a slowing of the beat of the mammalian heart in correlation with the diminished oxidations then occurring in the body generally, and its consequently diminished nutritional demands.

There are still other reasons why the direct application to the mammalian heart of the results of experiments upon frogs is unsatisfactory. It has been shown (4) that the muscular tissue of the amphibian heart differs considerably in histological characters from that of the mam-

malian: with this difference in minute structure quite important functional differences may be associated. Moreover, the mammalian heart is known to be far more under the control of extrinsic nerve centres than is that of the frog. Though the heart of the latter animal receives cardio-inhibitory fibres through the vagus, their centre of origin is not usually in action, as shown by the fact that cutting the vagi does not lead to pulse-quickening; exactly the reverse and to a very marked extent is the case in the dog (see especially V. Bezold) (5), and also in man as shown by the phenomena observed in cases of atropin poisoning. In addition, the mammalian heart receives from the cerebro-spinal centre accelerator nerve fibres, and the existence of any such pulse-quickening fibres in connexion with the frog's heart is at present doubtful. Consequently, bearing in mind that greater division of physiological duties which characterises the higher animal, we may justifiably doubt whether the simple relation of higher temperature (within limits) and quicker pulse found in the frog and dependent only on the properties of the heart itself, may not be entirely absent in the isolated heart of the higher animal, which we know to have its rate of beat under normal circumstances controlled by a highly specialized set of extrinsic nerve centres.

The above considerations, taken in connexion with the fact that "fever" can hardly be said to exist in an animal with so variable a normal temperature as the frog exhibits, made it very desirable to study directly the influence of temperature variations upon the pulse rate of the mammalian heart.

The experiments hitherto made upon mammalia do not really solve the question whether the quicker pulse of the warmer animal is due to a direct or an indirect action (*i. e.*, one exerted by extrinsic nerve centres) upon the heart. Bernard, Walther, Horwath, and no doubt others have found a slow pulse in artificially cooled animals; the same phenomenon has been observed in hibernating mammals during their winter sleep. As regards the effect of heightened temperature upon the pulse rate, Brunton (6) has shown that when rabbits are heated the heart beats quicker. But when a whole animal is warmed or cooled we are not justified in concluding that because the heart beats quicker or slower therefore the temperature change has directly influenced the rhythm of that organ. Not only may temperature changes indirectly affect the heart through its extrinsic nerves, but they may also so alter tissue metamorphosis in various organs as to essentially modify the composition of the blood flowing through the heart; and we know that very slight alterations in the chemical compo-

position of that liquid may profoundly influence the heart. Before we are entitled to state positively that changes of temperature directly influence the rhythm of the heart of the warm-blooded animal, we must have data based on experiments made with the hearts of such animals cut off from all possible control through extrinsic nerve centres, and supplied with nutriment of constant composition. The only experiments known to me which approach the fulfilment of such conditions are those made by several observers (Schenk (7), Wernicke (8), Cleland (9)) on the influence of temperature changes upon the rate of pulsation of the hearts of embryo chicks during the first three days of incubation. Such experiments afford, however, even a less safe ground for conclusions as to the adult mammalian heart than do the experiments upon frogs' hearts above referred to. The heart of three-day chick embryos is but a protoplasmic mass, little differentiated, presenting neither definite muscular nor nervous tissue, and without any developed controlling extrinsic nerves. From the fact that such a mass of hardly-differentiated embryonic cells contracts more frequently when warm than when cold, we cannot safely conclude that the adult heart, with its fully developed muscular and nervous tissues, and placed under the governance of nerve centres located outside it in the body, would, if isolated, respond in like manner to similar temperature changes.

While experiment upon the isolated hearts of frogs, fishes, and bird embryos, combined with the changes in the pulse rate observed when mammals are heated or cooled, have led to a general consensus of opinion among physiologists that gradual and moderate increases of temperature quicken the mammalian pulse by direct action upon the cardiac tissues, and moderate diminutions of temperature similarly slow the pulse, the proof that the action of such temperature changes was exerted directly upon the heart itself did not seem satisfactory, for the reasons above stated. Hence the investigation described in the following pages was undertaken.

THE METHOD.

The fundamental idea upon which all my work on the isolated mammalian heart has been based is to occlude all vessels of the systemic circulation except those supplying the heart itself, while leaving the pulmonary circulation intact. The heart and lungs being supplied with blood alone retain their vitality; all extraneous nerve centres getting no blood soon die with the remainder of the animal. Moreover, the blood supplied to the heart passes through no organ of the body but the lungs,

and in these it undergoes simple and well understood changes ; no sudden chemical alteration in it due to the products of the abnormal activity or commencing death of muscle, gland, or brain is possible. As the blood flows around through heart and lungs time and again, it no doubt experiences a gradual deterioration due to loss of foods and gain of wastes from those organs ; but this change is gradual and uniform, and if a sufficient quantity of blood be used, the accumulation of wastes (carbon dioxide being carried off by the lungs as in normal conditions) and the deterioration in nutritive quality do not for some hours alter its constitution to an extent which in any way interferes with the forcible, regular, and normal beat of the heart. The means adopted for renewing the blood circulating through heart and lungs, as also for maintaining constant arterial and venous pressures and for regulating the temperature of the blood, not having as yet been published in detail, and the method also having been much modified since the preliminary account was published, it is necessary to describe with some minuteness the operation of isolating the heart and the apparatus employed for subsequently keeping it alive under approximately normal and readily controllable conditions. I do this the more readily as the present form of the apparatus is the result of more than a year's experience and the accumulated improvements suggested by several workers (among whom special acknowledgment is due to my friends and pupils W. H. Howell and F. Donaldson), so that it now leaves little to be desired in the convenience with which it admits of keeping a heart under conditions in which venous pressure, arterial pressure, and temperature are readily ascertained and controlled. So far as the present series of experiments (those relating to the effect of temperature changes upon the pulse rate of the isolated heart) is concerned, dogs only have been used, and defibrinated strained calf's blood has been the medium employed to nourish the isolated heart.

The animal having been placed under the influence of chloroform, ether, morphia, or curare, the further course of an experiment was as follows :—

After tracheotomy the pneumogastro-sympathetic trunks were divided on each side of the neck with the object of saving the heart from the results of the powerful excitation of the cardio-inhibitory centre in the medulla oblongata, which usually occurs later, when the blood supply of the brain is cut off. A cannula was also placed in the cardiac end of each common carotid artery, the arteries being clamped on the cardiac sides of the cannulæ. Next, the first pair of costal cartilages and the bit

of sternum lying between them were cut away, and artificial respiration commenced; then the internal mammary arteries were tied as they pass forwards from the subclavians to the breast bone. The whole front and sides of the thorax were next cut away, and the right subclavian artery dissected out and tied just above the point at which it separates from the right carotid. The superior vena cava was then prepared, and ligatures placed loosely around it ready for subsequently occluding the vessel and tying in a cannula.

Proceeding now to the left side of the chest, the subclavian artery is ligated, and, the left lung being gently held aside, the aorta is isolated and cleared near the diaphragm. A ligature is placed loosely around the vessel, just beyond its arch, and a strong clamp tightened on it to the distal side of this ligature. An aperture having been made in the thoracic aorta, near its posterior end, a cannula of the form represented in Plate 48 [Plate 3 of this volume], Fig. 4, and filled with defibrinated strained calf's blood, is inserted into the vessel, and, the aortic clamp being removed, is pushed up to the left end of the aortic arch, where the ligature above-mentioned is tied tightly around it. These aortic cannulas are made of thin brass tubing, and are kept at hand of several sizes, so that one can always be found which fits tightly into the aorta of the animal and is closely clasped by the elastic walls of that vessel. The cannula has on its distal end the bit of rubber tubing, *v*, on which is the clamp, *w*, which is screwed tight when the tube is filled with defibrinated blood before its insertion into the artery.

So far all the systemic arteries but the coronaries of the heart are occluded. Each common carotid has a cannula in it; both subclavians are ligated below the point at which they give off any branch, and the aortic cannula is tied in at a level of the vessel, just beyond its arch, at which it has given off no bronchial or intercostal branches.* As one consequence, violent dyspnoëic symptoms usually occur in spite of the steadily maintained artificial respiration, being of course due to the want of a supply of fresh blood to the respiratory nerve centre. To complete the preliminary operation the inferior vena cava is tied above the diaphragm, and the right lung being pushed towards the median line, the vena azygos is ligated near its junction with the superior cava; the latter

* Sometimes in young dogs a minute branch is given off from the innominate artery to the thymus. This was sometimes tied, but usually neglected, as it is difficult to get at, and the amount of blood drained off by it is trivial, and when both venæ cavæ are tied cannot get back to the heart.

vessel is then tied below the point where the innominate and internal mammary veins join it by tightening one of the ligatures already described as placed loosely around it.

The next step is to wash out the blood contained in the heart and lungs, and replace it by defibrinated blood. For this purpose the cannula *z* (Plate 48 [Plate 3 of this volume], Fig. 3), connected with the Mariotte flask *U*, filled with defibrinated calf's blood at the temperature 38° C., is inserted into the cardiac end of the superior cava and tied there. The clamp on the tubing connecting the flask with the cannula is opened, and blood from the flask allowed to enter the right auricle. The clamps on each carotid, and on the aortic cannula, are then opened in turn for a short time so as to wash out all blood already in heart and lungs, and replace it with the defibrinated blood.

This having been done, and the clamps again closed, the animal, still tied on the dog-holder, is transferred to the warm moist chamber represented in outline in Plate 48 [Plate 3 of this volume], Fig. 1; in this chamber it is thenceforth fed steadily with defibrinated blood of known temperature, supplied at a known and controllable pressure, and from the chamber it pumps out blood against a known and readily varied aortic resistance. The structure, contents, and preliminary preparation of the warm chamber have next to be described. It is 125 centims. long, 65 centims. wide, and 65 centims. high. It has no bottom, but when in use sits in a shallow iron trough (not represented in the figure) filled with water and raised on supports which admit of Bunsen burners being placed under it, by whose means the air in the chest is kept moist and warm. The roof, sides, and the end, *A*, are glazed; the end, *B*, is of wood, and perforated by apertures through which several tubes pass. The object of glazing most of the walls of the chamber is to enable a ready view to be had of what is going on inside it; this is apt to be interfered with by condensation of water on the glass during the course of experiment; this drawback may, however, be nearly entirely obviated by smearing the inside of the glass with glycerine.

In the chest are two Mariotte's flasks, *C* and *D*, each of a capacity of about four litres. The flasks are entirely similar in all respects, but for the sake of clearness in the diagram the tubes only have been represented in connection with *C*, while the water-jacket which surrounds each flask is only indicated with *D*. This jacket, *E*, is merely a cylindrical tinned-iron bucket, somewhat wider than the flask. It is filled with water, and has, in connection with it, a syphon by which it can be readily emptied,

and a supply tube through which it can be filled. The syphon and supply tube have been omitted in the figure. Their ends pass outside the warm chamber, so that the water in the jackets can be changed without opening the box. As the flask empties of blood when in use, it tends to float up in the water of the vessel *E*. This is prevented by the collar *a*, which fits round the neck of the flask, and is attached by the bars *b, b*, to the upper edge of *E*.

In connexion with *C* are shown the tubes which pass through the air-tight cork of each Mariotte's flask. These are four in number. Two (*c, d*) are used when the flask is to be filled with blood; the other two (*e, f*) are employed when the flask is at work supplying the heart. When *C* is to be filled, the tubes *e* and *f* are closed by clamps or stopcocks put on the pieces of rubber tubing attached to their upper ends. The clamp *g* on the rubber tube attached to the upper end of *d* (which tubing, as shown in the figure, passes through an aperture, *G*, in the roof of the chamber) is opened, as is also the stopcock *h*, which is placed on the course of the tube leading from *c* to the funnel *F*. Meanwhile the corresponding stopcock *h'*, on the tube leading to the flask *D*, is closed. Defibrinated blood poured into *F* then enters the flask *C* through *c*, and the air which it displaces is driven out through *d*. *C* having been four-fifths filled, the stopcock *h* and the clamp *g* are closed, and the clamp *i* opened.

From the tube *f*, which dips deepest into the flask *C*, leads the rubber tube *k*; this passes through the end *B* of the warm chamber, and the next part of its course is shown in Plate 48 [Plate 3 of this volume], Fig. 2, where *k* is seen to lead to the stopcock *l*, which is connected with one limb of the Y-piece *m*, another limb of which is attached to the corresponding tube *k'*, leading from the flask *D*. The remaining limb of the Y-piece leads to the rubber tube *n*, which is seen again in Fig. 1, after entering the warm chamber. There *n* is seen to be continuous with the T-piece *o*, in the vertical limb of which is the thermometer *p*. Beyond the T-piece is the stopcock *q*, which ends in the rubber tubing *y*.

The flask *C* having been filled, we next go to the flask *D*, in connexion with which much of the details of the tubing have been omitted; but in all respects the flasks *C* and *D* and their connexions are similar. In the lettering of the figures whenever a connexion of *C* is indicated by a letter, the corresponding connexion of *D* is indicated by the same letter with a dash: *h* of *C* answers to *h'* of *D*; *d* of *C* to *d'* of *D*; *i* of *C* to *i'* of *D*, and so forth; so that a detailed description of the tubes connected with *D* is unnecessary.

To fill *D* the stopcock *h* is closed, and *h'* opened, as is also *g'*, while *i'* and *k'* are closed. Defibrinated blood poured into *F* then enters the flask *D*, and is added until that flask is about one-fourth filled. Then the stopcock *h'* is closed, and clamp *g'* screwed up, and the clamp *i'* opened. The further course of *k'* is seen in Plate 48 [Plate 3 of this volume], Fig. 2, where it is shown as joining *k* at *m*; it therefore ends also in the stopcock and rubber tubing *q* and *y*.

So far we have got the flask *C* four-fifths full of defibrinated blood and the flask *D* one-fourth full. It remains to fill the tube *f* and its fellow, and the system of tubes leading from both of them to the stopcock *q*, which during an experiment is connected with the superior vena cava, and has to supply the heart steadily with defibrinated blood. The tube *f* and its fellow have to act as syphons, and therefore the lower ends of *f* and *f'* must be above the level of the exit of *q*. To secure this, both flasks, *C* and *D*, are suspended by cords *r*, *r'*, which support each flask and its water-jacket. These cords pass over pulleys borne on a framework *H*, *I*, *J*, *K*, attached to the roof of the warm chamber, and each passes at its distal end round a fastener, *s*; by means of these cords the Mariotte's flasks can be raised and maintained at any desired level within the warm chamber. In the series of experiments here described both flasks were raised to the same height, although in Fig. 1, *C* has been drawn lower than *D* for the sake of showing their connexions more clearly in the drawing.

To fill the syphon connected with *C*, the stopcock *h* and the clamp *g* are closed; the clamp *i* is left open, as is the stopcock *l* (Plate 48 [Plate 3 of this volume], Fig. 2), while *l'* is kept shut. Then *q* (Fig. 1) is opened, and suction applied to the end of *y*; blood then flows out of *C* through *f*, while air enters through *e*; and this blood is supplied to *y* under constant pressure.

The cock *q* is now closed, as also *h'* and the clamp *g'*. The clamp *i'* is left open, the stopcock *l* (Plate 48 [Plate 3 of this volume], Fig. 2) closed, and *l'* opened. When *q* is now once more opened and suction applied to *y*, blood from *D* passes out by the tube *k'* and reaches *q* through the tube *n* (Fig. 1). *D* now, like *C*, behaves as a Mariotte's flask, and supplies blood to *y* under a constant pressure. If both flasks be raised to the same height above the level of the superior vena cava, with which *y* (as will be described immediately) is connected, we can supply a heart with blood from either flask at will. When the stopcock *l* (Plate 48 [Plate 3 of this volume], Fig. 2) is open and *l'* closed, the heart is fed from the flask *C*; when *l* is closed and *l'* opened, the blood is derived from *D*.

The flasks and the syphon tubes are filled as above described before the operation on the dog is commenced, and the stopcocks so arranged (*l* open and *l'* closed) that on opening *q* blood will be drawn from *C*.

The water-jackets around each flask being filled, the gas burners under the trough which supports the warm chamber are lighted. From time to time *q* is opened, and blood from *C* let flow through it. When the temperature of this blood, as indicated by the thermometer *p*, is about 37° C., the gas is turned low and the operation on the dog, described above, is proceeded with. While the flasks are warming *g* and *g'* are left open to allow some of the air in each flask to escape as it becomes expanded by the heat. Just before transferring the animal to the warm chest, *g* is screwed up, but *g'* left open; *h'* is also opened, and care is taken that *h* is shut. Under these circumstances *C* supplies blood to *y* when *q* is opened, while *D* (only one-fourth filled) is cut off from all connexion with *q*, but is ready to receive any blood poured into it from the funnel *F*, or flowing to it through the tube *L*.

When the animal is transferred to the chamber the portable Mariotte's flask (Plate 48 [Plate 3 of this volume], Fig. 3) is carried along with it by an assistant, and still supplies the heart with blood. A bit of brass tubing, *u* (Fig. 1), inserted into the lower end of the tube, *t*, is now connected with the distal end of the piece of rubber tubing, *v* (Plate 48 [Plate 3 of this volume], Figs. 1 and 3), attached to the distal end of the aortic cannula. The clamp *w* is then opened wide and the left ventricle pumps into and fills the tube *t*, from whose distal end the blood enters the funnel *x*; from this funnel it passes along *L* to the stopcock *h'* and thence to the flask *D*. The tube *t* has a bore at least as wide as that of the thoracic aorta of the animal, so that the heart pumps freely into it.

Next, the superior vena cava cannula *z* (Plate 48 [Plate 3 of this volume], Fig. 3) is slipped out of the rubber tube connecting it with the portable Mariotte's flask *U*, and quickly inserted into *y* (Fig. 1), care being taken that *y* is first filled with blood. The stopcock *q* being then opened, the heart is steadily supplied with blood from *C*. This blood, after traversing the lungs, is driven out of the left ventricle through *t*, and flows back to *D*, where it collects; accordingly as *C* empties *D* fills. When *C* is nearly exhausted the stopcock *h'* is closed, and also the clamp *g'*; *i'* is opened, as is also the stopcock *l'* (Plate 48 [Plate 3 of this volume], Fig. 2). Simultaneously *h* and *g* are opened, and *i* and *l* closed. *D* now becomes the feeding and *C* the recipient flask. When *D* in turn

is empty and *C* full the reverse steps to those above described make *C* the supplying and *D* the receiving flask; and so on as often as necessary in the course of an experiment. As all the clamps and stopcocks lie outside the warm chamber, the connexion of the flasks with the heart can be changed when desired without opening the chamber. During an experiment the tube *L* and the part of *t* outside the warm chamber are kept wrapped in raw cotton, as also the funnel *x*; and the openings *G* and *G'* are loosely covered with damp cloths.

To return to the steps immediately following the placing of the animal in the warm chest: *y* having been connected with the superior vena cava, the bellows hitherto used are disconnected from the tracheal cannula, and over this is slipped the delivery tube of one of the convenient respiration engines, driven by water pressure, manufactured by the Cambridge Scientific Instrument Company; this engine henceforth maintains uniform artificial respiration: its delivery tube is not represented in the figure, but enters the warm chest through an aperture in its back. Next a clamp is placed on the left subclavian artery, close to its origin. The vessel is opened between this and the ligature previously placed on it, and the bulb of a thermometer inserted into the artery. The clamp being removed, the thermometer is pushed down until its bulb projects into the aortic arch, and is then firmly tied in that position.

Finally the cannula *M* is placed in the right carotid of the dog and the cannula *N* in the left, and the clamps on those vessels removed. These cannulas are in connexion with the lead tubes *O* and *P*, which pass out through the end *B* of the warm chamber, and are connected with manometers. One manometer is a Fick's spring manometer, and is used for indicating the pulse rate; the other is a mean pressure mercury manometer, after Marey, having in its bend a stopcock which is nearly closed, so that each pulse beat is hardly visible on the tracing, but the mean pressure at any time in the carotid is indicated.* The pens of both manometers write over one another on the paper of a Ludwig's large kymograph. Below them, in the same vertical line, a chronograph pen inscribes seconds.

As soon as the carotid cannulas are inserted, the front of the warm chamber (which had been removed to admit of placing the animal inside

* In some of the earlier experiments only a mercury manometer was used. Owing to the doubts which have been cast upon the accuracy of this instrument when a very slow or a very quick pulse is to be recorded, the Fick manometer was subsequently added. It turned out, however, that this was unnecessary; the pulse rate recorded by both manometers was exactly the same.

and performing the above described manipulations) is replaced. The gas burners below the trough supporting the warm chamber are turned up, and a pause made before beginning observations until the air in the chamber, which has been much cooled while the front was away, is again heated up to about 38° C. ; and also until at least twenty minutes have elapsed since the complete occlusion of all the systemic circulation except that through the coronary vessels. Before the lapse of this time all signs of any activity of the extra-cardiac nerve centres cease, and the physiologically isolated heart is ready for experiment under conditions in which venous pressure, arterial pressure, and the temperature of the blood flowing through it are under very complete control.

By raising or lowering the Mariotte's flasks, *C* and *D*, venous pressure (*i. e.*, the pressure under which blood enters the right auricle) can be varied within wide limits. In the experiments described in the present paper it was always kept at that exerted by the weight of a column of defibrinated calf's blood 15 centims. in height, except when the contrary is expressly stated. Aortic pressure can be varied by sliding the support *Q*, which carries with it the exit of the aortic outflow tube, up or down the vertical rod *R*. Only the lower part of this rod is represented in the figure; its upper end reaches to the ceiling of the room. In most experiments the height of *Q* was arranged so that the mean pressure in the carotid was about 100 millims. of mercury. I had supposed before trial that I could in this way keep mean arterial pressure absolutely constant. But in spite of the small resistance offered by the wide aortic cannula and the wide system of tubes leading from it to the outflow point *S*, it turned out that the pressure as measured in the carotid (and therefore in the aortic arch) did not depend entirely and simply on the difference of level between the root of the aorta and the aperture of *S*. The left ventricle pumped out so much blood as to get up some elastic tension in the aortic arch and the arterial stumps still connected with it, and the pressure due to this was added to that dependent on the height of the column of blood against which the heart worked and on friction in the outflow tubes through which it was driven. So long as the heart works with sufficient force to pump blood up to and out of *S* the resistance due to the weight of the column of blood to be lifted remains the same; if the rate of flow be slower, the resistance, and therefore the increased pressure due to friction, will be diminished, but in such wide tubes probably only to a trivial extent. When, however, any cause, such as change in temperature, deterioration in quality of the blood supply, impediment in the

pulmonary flow, or gradual death of the isolated heart, influences the amount of blood pumped out in the unit of time by the left ventricle, then the elastic reaction due to distension of the stumps of the great arteries is altered. Hence, even while a heart is pumping blood freely out through the exit *S*, kept at a constant height, variation of arterial pressure, as measured in the carotid, may occur to the extent of 10 millims. of mercury pressure. Such variations will be noticed in some of the protocols of experiments given in this paper; but fortunately they in no way affect the question here considered, viz.: the influence of changes of temperature upon the rate of beat of the isolated heart. I have previously shown (2) that slow variations of arterial pressure between the limits of 30 and 150 millims. of mercury do not in the least influence the pulse rate of the isolated dog's heart, provided venous pressure and the composition and temperature of the blood be kept constant.

Venous pressure and, approximately, arterial pressure being kept uniform, the temperature of the blood alone was altered in the experiments below described. The variation was effected in two ways. First by pouring a little heated (50° C.) or cooled (10° C.) blood into the funnel *F*, from which it entered the flask not in use at that moment, and warmed or cooled the blood already in it. Then this flask was used to feed the heart and the other as the recipient, by opening and closing the proper clamps and stopcocks. This method was rarely used, as it sometimes produced secondary effects, due to the comparatively sudden changes of temperature in the blood supplied to the heart. A more gradual and uniform alteration in the temperature of the blood was secured by changing the water in the jackets around the Mariotte's flasks. Some hot water and some water cooled by ice to 5° or 10° C. were always kept at hand during an experiment. If a series of heating observations was to be made, some of the water already in the jackets was syphoned off, and replaced with warm, care being taken that the temperature never rose above 60° C., so as to avoid all risk of coagulating any of the proteids of the defibrinated blood: more hot water was added from time to time if necessary. To initiate a series of observations as to the effect of cooling, the iced water was of course employed. The best results were obtained when the temperature of the water in the jackets did not differ by more than 20° from the temperature of the blood in the flask. When either Mariotte's flask was in use the rapid bubbling through its contents of the air entering by the tubes *e* and *e'* ensured their thorough mixture.

Having waited, then, for the death of extrinsic nerve centres, and until the thermometer *p* had during some minutes indicated a tolerably even temperature, the water around the Mariotte's flasks was cooled or heated, and a series of observations commenced. The initial temperature usually lay between 37° and 38°, but, as will be seen in the experiment protocols which follow, was sometimes higher or lower. Tracings of arterial pressure and pulse rate were taken at intervals varying from one to five minutes. When the tracing was completed an assistant immediately opened a small door in the front of the warm chamber, and read off the temperature of the blood flowing through the heart.

As regards this temperature, the question arose which thermometer to use; that, *p*, in the inflow tube, or that pushed down the left subclavian to the aortic arch. The former gave the temperature of the blood flowing through the cavity of the right heart; the latter the temperature of the blood in the left auricle and ventricle and aorta, and accordingly in the coronary arteries supplying the cardiac capillaries. *A priori*, there seemed little doubt that it would be the temperature of this latter blood, brought as it was into close relation with every muscle fibre and ganglion cell in the heart, which would exert an influence on the cardiac rhythm, if any did. Experiment soon confirmed this. Both thermometers were read in several experiments, and it was always found that the pulse-rate changes followed much more closely the variations of temperature indicated by the instrument in the subclavian. In most cases, accordingly, only the reading of this thermometer was undertaken, as it was very desirable to reduce to a minimum the time during which the door of the warm chamber was open.

The temperature observed was written on the kymograph paper over the tracing, along with the time at which the latter had been taken. After a pause, another tracing was taken, time and temperature noted as before, and so on throughout the experiment, which was usually continued until the heart began to show symptoms of weakened or abnormal action.

The roll of tracings was subsequently gone over carefully, and on the graphic record of each observation periods of twenty seconds marked out; the pulses during that time were counted, and the mean arterial pressure measured. The results were then put in tabular form, the actual pulses counted being multiplied by three, so as to give the rate per minute instead of the number of beats in twenty seconds. In the "detailed results" given below, six such tables are printed; as curves

present very quickly and accurately to the apprehension the general outcome of long columns of figures, charts have also been constructed (Plate 49 [Plate 4 of this volume], giving the curves of temperature variation and pulse-rate change during two of these experiments.

DETAILED RESULTS OF EXPERIMENTS.

Before proceeding to the following tables, which give the actual figures as to pulse rate and temperature for several experiments, a few words of explanation are desirable with reference to some three or four points.

First, it will be noted that for normal temperatures (38–39° C. in the left ventricle of the dog, according to Claude Bernard) (10) the pulse is very fast. This is undoubtedly due to the section of both pneumogastrics, cutting off the heart from control by the extrinsic cardio-inhibitory centre, which is normally very active in the heart of the dog. Upon atropin paralysis of the peripheral pneumogastric connexions with the heart V. Bezold and Bloebaum (5) found in this animal the pulse rate sometimes increased 80 per cent. An increase of 80 per cent. above the average will more than account for the quickest pulse observed by me at normal temperatures.

Second, it will be seen that, quite independent of any changes of temperature, the heart beats slower towards the end of an experiment than it did at the beginning, although its action may still be regular and each pulsation powerful. This is undoubtedly due to altered nutrition resulting from the use of calf's blood, as it was not observed, or at least not until much later in my earlier experiments (2), when dog's blood was employed. In consequence of this gradual and progressive slowing of the pulse it might be objected in a cooling experiment that any observed diminution of the rate of heart beat was dependent on other conditions than cooling of the organ. To meet this objection, in most instances after a series of cooling observations a series of heating has been made on the same heart, and these show that in every case the heart beats much quicker when again warmed. This makes it clear that the slow pulse previously observed was not due merely to progressive malnutrition of the isolated heart, but was mainly dependent on the lower temperature to which the organ was exposed. Taking for example Experiment I, we find at 1 h. 34 m. P. M., the heart beat 246 times a minute at the temperature of 37.8° C. Forty-three minutes later (at 2 h. 17 m. P. M.) it beat only 217 times per minute at the temperature 38.1° C.; but meantime

the pulse rate, at 1 h. 57 m. P. M., had been down to 73 per minute, the temperature being 27.8° C. This slow pulse being followed twenty minutes later by one nearly three times as fast cannot of course have been conditioned by any progressive diminution of functional capacity dependent on the prolonged use of calf's blood; this becomes still more obvious when, later on in the same experiment, we find a second cooling accompanied by a slower pulse, and a second heating by a quicker.

Third, it may be noted that in no case does any one of the experiments given last longer than two hours, and that, with one exception (Experiment VI), it is stated that the observations had ceased because of some obvious abnormality in the heart's action. In my earlier experiments with isolated hearts a practically normal beat often lasted for four hours or longer. They were, however, carried out on a different plan, which allowed of the use of defibrinated dog's blood to nourish the heart. Instead of permitting the left ventricle to pump blood out through a wide aortic cannula, the only exit left was through a narrow cannula in one carotid, and, in correspondence with this fact, the tube supplying the superior cava was also narrow. In the present series of experiments the widest possible cannulæ were placed in the aorta and vena cava, and all the tubing attached to these, and the stopcocks upon it, had a bore as wide as that of the cannulæ. Under such circumstances the heart pumps round three or four litres of blood in a very few minutes, and with a smaller amount the stopcocks and clamps used to make the flasks *C* and *D* alternately feeding and recipient, would have to be changed at such short intervals as to make it impossible to carry on any uniform series of consecutive observations. With the original method 1000 to 1500 cubic centims. of whipped blood was enough for convenient use, and this quantity it was possible to obtain from dogs. When four litres or more of blood are wanted it becomes practically impossible to use dog's blood, and so some other had to be selected. After several trials calf's blood was chosen. This blood, however, nourishes the heart less satisfactorily, and hence the earlier indications of commencing death.

With respect to the choice of blood I add a few words which may be of aid to any one desirous to repeat my experiments. It is important to have it from quite young calves; that is to say, from animals which are still suckling: a point of itself of some interest when considered in connexion with the well known fact that the chemical composition of the urine of the nurslings of herbivora shows that their nutritional processes agree in the main with those of adult carnivora, and differ essentially

from those of the adults of their own species. In spite of all care I used to be frequently disappointed by the death of the isolated heart before any satisfactory number of observations could be carried out upon it, even in cases when I could think of no cause for the failure. Light broke upon me when the laboratory attendant, whose duty it was to bring the blood from the slaughter-house, remarked one day that it seemed to him that we nearly always got on better when he did not get the blood from "wharf calves." On questioning, I found that "wharf calves" was the term employed by Baltimore butchers to indicate animals which, though still young enough to yield veal, were of such age that they had long ceased to live on milk. Since the blood of such calves has been rejected the percentage of failures has considerably decreased. It is hardly necessary to add that care must be taken that no extraneous matter enters the blood during its collection. Baltimore butchers stun the calves and then cut their throats, and while the blood flows out vomiting frequently occurs and sends the contents of the stomach into the collecting pail. The blood from each animal has therefore to be collected separately, so that the quantity already obtained may not be rendered unfit for use by admixture with matters from the stomach of another animal.

Even with the best obtainable calf's blood, however, the results are not as satisfactory as with dog's blood. Not only does the heart die sooner, but other changes occur which shorten the time during which an experiment can be carried on. The most marked of these is lung oedema, which nearly always takes place in the course of an hour and a half, to such an extent as to seriously impede the pulmonary circulation and the aeration of the blood in the lungs. In consequence, the supply of blood to the left heart is hindered, and the right heart becomes gorged, and its auricle finally paralyzed; and this, of course, puts an end to an experiment. Another trouble which is apt to occur when calf's blood is used is considerable pericardial exudation, often to such an extent as to seriously interfere with the beat of the heart. This difficulty may, however, be readily avoided by cutting a small hole in the pericardium as soon as the heart is placed in the warm chamber. A third difficulty met with when calf's blood is employed is more serious. Many observers have noted on the isolated frog's heart, supplied with various nutrient liquids, a gradual increase in the bulk of the organ in the course of a prolonged experiment; this increase being due, apparently, to an alteration in the elastic modulus of the cardiac muscle. The same phenomenon is observed when a dog's heart is fed with calf's blood. Gradually the systolic size of the organ

increases, until at last, even at the height of its systole, the heart very nearly fills the pericardiac sac. During the subsequent diastole there is, therefore, but little opportunity for the organ to expand and receive blood. When this state of things takes place, one sees on the tracings that a good arterial pressure is still maintained, and that the heart rhythm is regular, but the height of each pulse curve is much diminished; and on looking at the exit (Plate 48 [Plate 3 of this volume], Fig. 1, *S*) of the aortic outflow tube, it is seen that the quantity of blood expelled at each systole is markedly decreased. If the heart be then examined it will be found so distended as to tightly fill the pericardium, and if the latter be carefully cut away the pulse rate remains unaltered; but the heart now does again nearly, or quite, its original work: the pulse curves on the tracing regain their previous extent, and the gush from the aortic outflow tube at each systole becomes as great as it was before the occurrence of the distension of the heart. The impediment to the heart's action, due to this expansion, may be avoided either by cutting away the pericardium before beginning a set of observations or by removing it later when it begins to interfere with the heart's action. Both methods have been used in the course of the experiments whose results are given in the present paper. In selecting special examples for publication it seemed best, however, to include, mainly, cases in which the normal state of things had been interfered with as little as possible; and in none of the tables which follow was the pericardium cut away before the commencement of the observations, and in only two cases (Experiments II and IV) during their progress. It seemed desirable to include these for the purpose of showing that, although the heart's effective work is much diminished when it has become so distended as to fill the pericardium, yet its rate and force of beat are unaltered.

The ill results of pulmonary œdema above described may be obviated to a great extent by pricking numerous holes in the lungs with a fine needle. This allows the liquid collected in the air cells and small bronchial tubes to escape, and relieves the pressure on the pulmonary capillaries, while it also allows air to reach the air cells. This operation in no way affects the general result so far as pulse rate is concerned, the chief objection to it being the loss of blood due to trickling from the wounds. To avoid objections, only one case (Experiment IV) in which the lungs were so pricked is included in the experiments detailed in the present communication.

Before leaving this question of the troubles attending the use of calf's blood, I may state that some considerable experience has led me to the conclusion that the drawbacks more than balance the advantages, at least in so far as most experiments are concerned. If I had to repeat the investigation here described, I should certainly tie the aorta just beyond its arch, and connect the outflow tube *t* with the left carotid instead of with the aorta; pulse rate and mean pressure could then be recorded by manometers placed in the right subclavian and carotid arteries, and in correlation with the narrowed outflow orifice, the feeding tube, *n*, of the heart could be narrowed. Under such circumstances much less blood would be pumped around in a given time, and it would be possible to obtain the quantity requisite for carrying on an experiment from dogs instead of from calves. Pulmonary œdema and loss of cardiac elasticity would then occur much later. Of course in other cases, as when, for example, the greatest amount of blood which could be forced out from the left ventricle in a systole was to be sought, or the work done by the left ventricle under varying conditions, it would be necessary to use the wide tubes and stopcocks which I have above described, and these would almost necessarily lead to the use of other than dog's blood for the nourishment of the isolated heart.

Fourth, as a final remark before proceeding to give experiment protocols, I call attention to the fact that in the following tables it will be seen that now and then a slight rise of temperature occurs in the course of a cooling experiment, or a slight fall in the course of a heating. Such breaks were nearly always due to the necessity of changing the feeding Mariotte's flasks from time to time. While *C* is emptying and *D* filling, it is not possible to ensure that when *D* is in turn connected with the heart, the blood in it shall always be exactly of such temperature as to fit into the series of cooling or heating observations which had been carried on with *C*. An endeavor was always made to make the observations with the alternate flasks regularly consecutive as regards changes of temperature, and it will be seen that, in most cases, this was attained. When it was not, the resulting temporary rises or falls of temperature serve only to verify the general result; a slight and transitory heating in the course of a general cooling experiment quickens the pulse, and *vice versa*.

I now give, in tabular form, the results of six experiments.

EXPERIMENT I.

April 24, 1882.—The dog used weighed 5790 grms. and was chloroformed during the operation of isolating the heart. Venous pressure throughout equal to that exerted by a column of defibrinated calf's blood 15 centims. in height. Arterial pressure, measured in the right carotid, varied between 97 and 104 millims. of mercury. All the systemic vessels but those of the coronary system of the heart were occluded at 12 h. 50 m. P. M.

Number of observation.	Time, P. M.	Temperature, centigrade, indicated by thermometer passed through left sub-clavian to aortic arch.	Pulse rate per minute.	Remarks.
	h. m.			
1	1 33	37.5	240	
2	1 34	37.8	246	
3	1 38	35.5	204	
4	1 40	34.8	191	
5	1 42	33.8	178	
6	1 44	32.0	153	
7	1 46	31.5	148	
8	1 48	30.5	129	
9	1 50	29.9	119	
10	1 52	29.0	105	
11	1 54	28.0	82	
12	1 57	27.8	73	
13	1 58	28.3	79.5	
14	2 01	29.0	83	
15	2 04	29.6	88	
16	2 06	31.1	129	
17	2 07	33.0	155	
18	2 08	33.9	168	
19	2 10	35.5	190	
20	2 11	37.0	207	
21	2 13	37.9	223	
22	2 14	36.8	203	
23	2 15	37.3	209	
24	2 17	38.1	217	
25	2 19	39.5	233	
26	2 20	40.5	240	
27	2 22	39.8	225	
28	2 26	39.5	219	
29	2 28	38.0	198	
30	2 30	36.8	181	
31	2 31	36.0	179	
32	2 34	34.5	159	
33	2 36	34.5	160	
34	2 38	32.8	131	
35	2 39	31.8	114	
36	2 41	30.8	87	
37	2 43	30.3	84	
38	2 45	30.5	80	Irregular.
39	2 46	30.8	81	Regular.
40	2 47	31.3	84	Slightly irregular.
41	2 49	31.5	87	Regular.
42	2 51	32.1	118.5	

EXPERIMENT I.—*Continued.*

Number of observation.	Time, P. M.	Temperature, centigrade, indicated by thermometer passed through left sub-clavian to aortic arch	Pulse rate per minute.	Remarks.
43	h. m. 2 53	32.5	126	The pulse now became very irregular, and its rate fell rapidly in spite of a supply of warmer blood to the heart.
44	2 55	33.1	135	
45	2 59	36.5	184	
46	3 00	36.3	160	
47	3 02	35.8	167	

The results of Experiment I are represented graphically on Plate 49 [Plate 4 of this volume]. Each division along the abscissa corresponds to two minutes of time. The level of the abscissa line answers to a temperature of 25° C. and to a pulse rate of 60 per minute. The continuous curve represents the pulse variations during the experiment. Each division on the height of ordinates drawn from any point of the pulse curve to the abscissa answers to ten pulse beats more than 60 per minute. The dotted curve represents the temperature variations. Each division of height in ordinates drawn from it to the abscissa represents one degree centigrade above 25°. It will be observed that the curves of temperature and pulse rate fall and rise together throughout the experiment.

EXPERIMENT II.

April 27, 1882.—The dog weighed 5550 grms. Chloroform and ether administered during the operation of isolating the heart. Venous pressure that exerted by a column of defibrinated calf's blood 15 centims. in height. All the systemic vessels but those supplying the heart itself were ligated at 3 h. 10 m. P. M. The animal was transferred to the warm chamber at 3 h. 15 m. P. M., and then decapitated and a stout wire run down the spinal canal as far as the lumbar region before any observations as to pulse rate were made.

EXPERIMENT II.

Number of observation.	Time, P. M.		Arterial pressure in left carotid, in millims. of Hg.	Temperature in aortic arch.	Pulse rate per minute.	Remarks.
	h.	m.				
1	3	30	100	38.0	237	Since last observation one carotid cannula had slipped out and been replaced.
2	3	33	102	37.9	234	
3	3	40	99	38.5	241.5	
4	3	42	98	38.5	244	
5	3	44	98	41.5	273	
6	3	46	101	40.5	258	
7	3	47	99	40.9	261	
8	3	48	100	42.0	267	
9	3	52	100	42.0	265.5	
10	3	53	99	42.5	265.5	
11	3	54	100	42.5	250	Flask changed since last observation; hence the rapid alteration of temperature.
12	3	55	97	39.5	222	
13	3	57	97	37.0	198	
14	3	58	97	36.0	189	
15	3	59	97	35.5	175.5	
16	4	00	98	34.7	169	
17	4	01	97	34.0	162	
18	4	02	98	34.0	165	
19	4	04	98	33.9	153	
20	4	05	99	32.9	144	
21	4	06	100	32.5	140	Pericardium cut away since last observation.
22	4	09	98	31.7	124.5	
23	4	11	100	30.1	105	
24	4	12	100	30.0	105	
25	4	15	101	29.9	97	
26	4	17	101	29.5	88	
27	4	19	101	29.0	84	
28	4	21	103	28.5	76	
29	4	23	104	27.5	75	
30	4	26	108	27.3	66	
31	4	27	112	28.0	66	Pulse irregular. Pulse regular. Heart's beat now became very irregular and experiment was discontinued.
32	4	30	108	28.1	69	
33	4	32	108	29.5	111	
34	4	33	108	31.5	129	
35	4	34	107	32.5	162	
36	4	35	109	34.0	183	
37	4	36	105	35(?)	150	
38	4	37	107	34.1	144	
39	4	39	105	33.5	135	
40	4	41	106	33.5	133.5	
41	4	43	105	34.0	135	
42	4	44	102	34.7	117	
43	4	46	

Experiment II presents two points of special interest: in the first place the brain was removed and the cervical and dorsal spinal cord destroyed before the observations commenced, so that an additional security was obtained that no cerebro-spinal centres were influencing the pulse rate. In the second place it is one of the cases in which the heart became considerably distended during the course of the experiment, so

that the pericardium had to be cut away. As will be seen, this did not at all affect the general result.

EXPERIMENT III.

May 3, 1882.—Dog weighed 6000 grms. Narcotised by subcutaneous injection of acetate of morphia before the operation of isolating the heart was commenced. Venous pressure at first that due to a column of whipped blood 10 centims. high, and afterwards to a column 15 centims. in height. Heart isolated at 12 h. 55 m. P. M.

Number of observation.	Time, P. M.		Carotid pressure in millims. of Hg.	Temperature, C.° in aortic thermometer.	Pulse rate per minute.	Remarks.
	h.	m.				
1	1	20	110	34.5	151.5	Venous pressure 10 centims.
2	1	23	110	34.9	162	
3	1	25	110	36.1	185	
4	1	27	110	36.1	186	
5	1	29	110	37.9	211	
6	1	30	110	39.3	225	
7	1	31	110	40.0	232.5	
8	1	33	111	40.5	235	
9	1	35	110	40.3	222	
10	1	38	110	38.5	202.5	
11	1	41	109	37.0	184.5	Venous pressure raised to 15 centims. between observations 10 and 11.
12	1	43	110	36.9	195	
13	1	45	110	35.5	168	
14	1	46	112	33.9	152	
15	1	49	110	33.5	156	
16	1	51	110	32.7	142	
17	1	53	110	32.1	129	
18	1	55	111	30.0	102	
19	1	57	111	29.1	94.5	
20	1	58	110	28.9	87	
21	1	59	96	28.0	67.5	Heart weakens and ceases to pump round before next observation.
22	2	06	42	31.5	63	
23	2	08	Heart beat irregular and experiment discontinued.
24	2	10	

EXPERIMENT IV.

May 10, 1882.—Dog weighed 10,300 grms. Narcotised by subcutaneous injection of acetate of morphia before commencing the operation of isolating the heart. Venous pressure that due to a column of defibrinated calf's blood 15 centims. in height. Heart isolated at 12 h. 25 m. P. M.

EXPERIMENT IV.

Number of observation.	Time, P. M.		Carotid pressure in millims. of Hg.	Temperature in aortic arch.	Pulse rate per minute.	Remarks.
	h.	m.				
1	12	45	118	34.1(?)	158	It seems almost certain that the reading of the thermometer in observation 1 was a degree out, and should be 35.1°.
2	12	47	117	34.5	151	
3	12	49	116	35.1	157	
4	12	51	116	35.5	156	
5	12	53	116	37.1	183	
6	12	54	116	39.0	195	
7	12	55	116	38.0	180	
8	12	56	116	38.3	181.5	
9	12	58	116	38.5	184.5	
10	12	59	116	38.5	183.0	
11	1	00	116	38.0	172.5	
12	1	02	112	37.5	166.5	
13	1	03	113	36.5	157.5	
14	1	05	112	35.0	137.0	
15	1	06	114	34.0	127.5	
16	1	08	114	33.5	126.0	
17	1	09	112	33.5	126.0	
18	1	11	111	32.7	114	
19	1	13	110	31.9	108	
20	1	14	111	31.5	102	
21	1	15	113	31.0	99	Lungs pricked since last observation.
22	1	17	113	30.5	92	
23	1	20	112	31.5	110	
24	1	22	112	32.5	119	
25	1	24	110	33.9	133.5	
26	1	27	110	34.0	129	
27	1	30	113	34.5	139.5	
28	1	32	114	35.0	140	
29	1	34	114	35.5	148	
30	1	37	(?)	36.5	179	Pericardium cut away since last observation.
31	1	38	101	38.0	192	
32	1	39	105	39.0	198	
33	1	40	107	39.6	199	
34	1	42	108	39.0	189	After this the heart suddenly ceased to pump round, and its right auricle was seen to be paralysed. The lungs were extremely œdematous.

The chart on Plate 49 [Plate 4 of this Volume] represents graphically the results of the preceding experiment.

EXPERIMENT V.

May 22, 1882.—Dog weighed 5605 grms. Chloroform administered while the heart was being isolated. Venous pressure at first that due to a column of defibrinated calf's blood 10 centims. in height, then doubled. Temperatures taken both in inflow tube (by thermometer *p*, Plate 48 [Plate 3 of this volume], Fig. 1) and in the aortic arch by a cannula thrust down the left subclavian artery. Heart isolated at 1 h. 30 m. P. M. The mean temperature given in the sixth column is obtained by adding together the inflow and outflow temperatures and dividing by 2. It does not really represent the mean temperature of the heart, as while the inflow temperature is that of the blood in right auricle and ventricle, and the outflow (aortic) temperature that in left auricle and ventricle, the latter is also the temperature of the blood circulating in the walls of the heart itself.

Number of observation.	Time, P. M.	Carotid pressure in millims. of Hg.	Inflow temperature.	Outflow (aortic) temperature.	Mean temperature.	Pulse rate per minute.	Remarks.
	h. m.						
1	1 55	94	36.3	36.5	36.4	227	Venous pressure 10 centims.
2	2 00	94	37.3	37.3	37.3	234	
3	2 05	94	37.3	37.5	37.4	238	
4	2 10	94	37.5	36.7	37.1	225	
5	2 12	93	38.5	37.5	38.0	231	
6	2 14	96	39.5	39.0	39.2	249	Venous pressure raised to 20 centims.
7	2 16	96	38.0	38.5	38.2	244.5	
8	2 18	96	38.5	38.3	38.4	238.5	
9	2 20	97	39.0	38.7	38.8	241	
10	2 23	94	39.1	39.0	39.0	244	
11	2 25	94	40.3	39.7	40.0	249	Pulse very suddenly slowed and became somewhat irregular and experiment discontinued.
12	2 27	95	40.7	40.1	40.4	252	
13	2 30	97	40.0	39.9	39.9	252	
14	2 33	92	40.0	39.7	39.8	243	
15	2 35	92	40.0	39.5	39.7	233	
16	2 38	52	(?)	(?)	...	102	

EXPERIMENT VI.

May 22, 1882.—Dog weighed 1140 grms. Chloroformed while the heart was being isolated. Venous pressure throughout that due to a column of defibrinated calf's blood 20 centims. in height. Heart isolated at 3 h. 40 m. P. M.

EXPERIMENT VI.

Number of observation.	Time, P. M.	Carotid pressure in millims. of Hg.	Temperature of aortic blood.	Pulse rate per minute.	Remarks.
	h. m.				
1	4 05	101	37.5	173	
2	4 07	99	36.9	170	
3	4 09	98	36.7	163.5	
4	4 14	98	36.7	156	
5	4 17	97	36.0	145.5	
6	4 20	97	35.1	132	
7	4 22	98	34.6	126	
8	4 23	98	34.1	117	
9	4 25	99	33.5	114	
10	4 28	97	33.0	108	
11	4 30	97	32.3	105	
12	4 32	96	32.5	91	
13	4 33	98	31.5	85	
14	4 34	98	31.1	85.5	
15	4 36	96	30.5	73.5	
16	4 37	96	30.1	76	
17	4 39	98	29.9	68	
18	4 41	95	29.5	69	
19	4 43	98	29.3	61	
20	4 45	98	28.9	63	
21	4 47	96	28.7	55.5	
22	4 51	98	28.7	61	
23	4 55	94	28.5	54	
24	4 57	97	28.5	54	
25	5 00	97	28.3	48	
26	5 03	96	28.1	52	
27	5 05	96	27.7	43	
28	5 08	94	27.5	28	Pulse irregular but each beat powerful.
29	5 10	90	27.6	24	
30	5 12	90	27.6	24	
31	5 14	92	27.6	21	
32	5 16	82	27.3	19.5	Heart ceases to pump blood to top of aortic outflow tube.
33	5 18	67	27.3	21	
34	5 21	58	27.1	21	
35	5 23	52	27.3	18	
36	5 25	49	27.3	18	
37	5 27	51	27.5	21	
38	5 30	45	28.0	19.5	
39	5 35	70	28.0	40.5	Pumps round again.
40	5 37	92	28.3	48	
41	5 40	93	28.5	58	
42	5 42	94	28.7	66	
43	5 43	96	29.1	73	
44	5 45	95	29.9	76	
45	5 49	93	30.5	82.5	
46	5 51	93	31.5	99	Experiment now discontinued. Heart still beating regularly and forcibly.

The above experiment is remarkable for the very slow pulse observed throughout. Even at 37.5° the pulse was only 173 per minute, whereas in most isolated hearts it is over 200 at that temperature. When the temperature was brought down to near 27° the extraordinary slow pulse of 18 per minute resulted; a pulse so slow that although each beat was powerful, the left ventricle pumped out in each minute less blood than was drained off from the aorta by the coronary arteries, so that the level of the blood in the aortic exit tube fell lower and lower until the carotid pressure finally came down to 41 millims. of mercury. On again heating the blood supplied to the heart the organ regained completely its functional activity. Before the cooling (observation 13) the pulse rate at the temperature 31.5° was 85 per minute, and pressure in the carotid was 98 millims. of Hg. After the cooling, on again heating, we find at the same temperature (observation 46) a pulse of 99 per minute and a carotid pressure of 93 millims. of mercury. It is unfortunate that the experiment was not continued, but the exceptionally slow pulse obtained was not recognised until the tracings were counted out the next day, and as it was the second experiment of the same date I was fatigued and stopped so soon as I had satisfied myself that reheating the blood had quickened the pulse, instead of going on as usual until the heart began to show signs of commencing death.

CONCLUSIONS.

As regards the question which the preceding experiments were primarily designed to answer, their results are decisive. They make it clear that the mammalian heart when quite cut off from all extraneous nervous control, and when supplied with blood which has not been altered in composition by products of abnormal tissue change, due to abnormal heating or cooling of other organs of the body, does beat quicker when warmer blood is supplied to it, and slower when it gets cooler blood. In this respect the heart of the dog behaves quite like that of the frog. In spite of the greater division of physiological duties in the body of the mammal, and the greater subjection of the mammalian heart to control from special extrinsic nerve centres, the dog's heart in its own neuro-muscular apparatus is so constituted as to have its rate of periodic activity directly controlled by its temperature. To account for the quick pulse of fever we need therefore assume no paralysis of extrinsic cardio-inhibitory nerve centres and no excitation of cardio-accelerator. The warmed mammalian heart beats quicker because of its own physiological properties.

In addition to the above main question, several subsidiary points have some light thrown upon them.

(1.) The rate of beat of the mammalian heart does not directly depend upon the temperature of the blood reaching the right auricle, except in so far as this influences the temperature of the blood pumped out by the left ventricle and supplied to the coronary arteries. It is not the temperature of the blood in its cavities which influences the rate of beat of the dog's heart, but the temperature of the blood sent to its capillaries. In other words, temperature changes do not influence the pulse rate by stimulating afferent nerves in the endocardium which then act upon cardio-motor ganglia, but they act directly upon the muscle fibres or nerve cells of the organ.

(2.) A second subsidiary fact illustrated by the preceding experiments is that the heart of the dog can be nourished for some time and kept in a good state of functional activity when fed only with calf's blood; but this blood is far less satisfactory than dog's blood, its use soon leading to pulmonary œdema and alteration of the elastic modulus of the cardiac muscular tissue.

(3.) As a third point of interest it may be noted that no clotting takes place in defibrinated blood circulated for some hours through the living heart and lungs. Such blood contains an abundance of fibrino-plastin (para-globulin) and fibrin ferment, together with the quantity of salines necessary for the formation of fibrin if fibrinogen were present. Fibrinogen, therefore, is produced in other organs of the body than heart and lungs. By further experiments in which the isolated heart shall be connected with various other isolated organs and pump blood through them I hope to discover in what organs fibrinogen is produced.

It would have added much to the interest of the research described in the preceding pages if determinations had been made as to the highest and lowest temperatures at which the dog's heart would beat, and I had hoped when commencing the investigation to have discovered those temperatures. It turned out, however, that with the method of work described in the preceding pages this was not possible. When the heart is considerably cooled, for example, it pumps around so little blood that the amount sent out at each systole of the left ventricle is less than that carried off by the coronary arteries. Under these circumstances the coronary system is mainly supplied with warm blood derived from the column of liquid accumulated in the aortic outflow tube (Plate 48 [Plate 3 of this volume], Fig. 1, *t*). As a consequence, the blood in the right

heart comes to be of a very different temperature from that circulating in the cardiac capillaries, and the result is irregular and inco-ordinate action of the right and left sides of the heart, and a total cessation of all circulation. Quite similar results follow warming of the blood supplied to the right auricle to near the death temperature. Consequently I have not been able to discover the temperature limits of the vitality of the dog's heart. Some preliminary experiments, carried on in a different manner, lead me to hope that the question as to the highest and lowest temperature at which a dog's heart will beat can be solved; but my work in that connexion is not yet ready for publication.

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Fig 2.

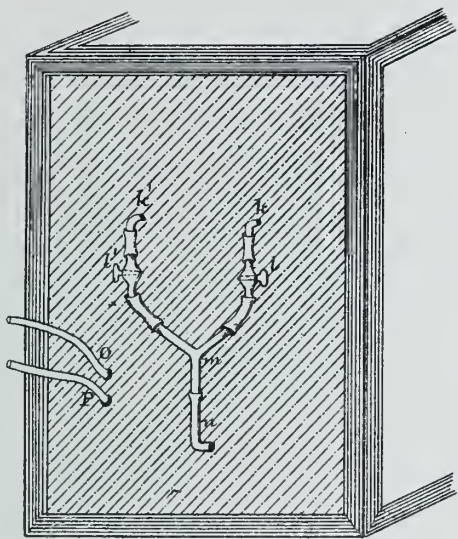


Fig 3.

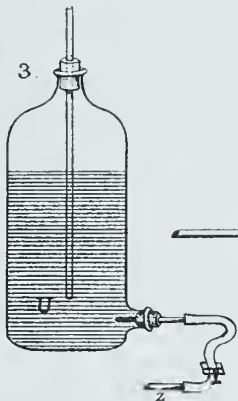


Fig. 4.

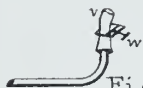
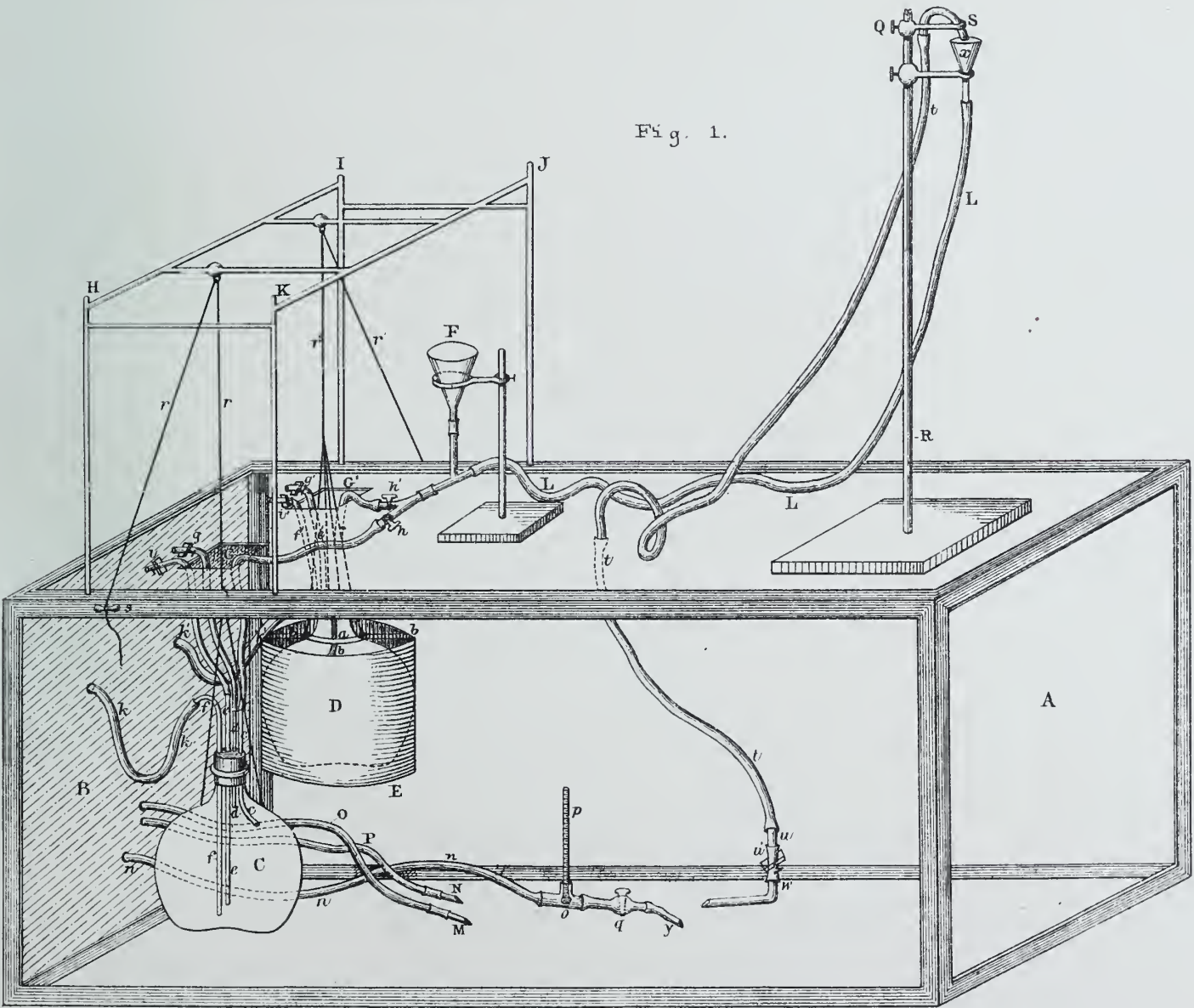
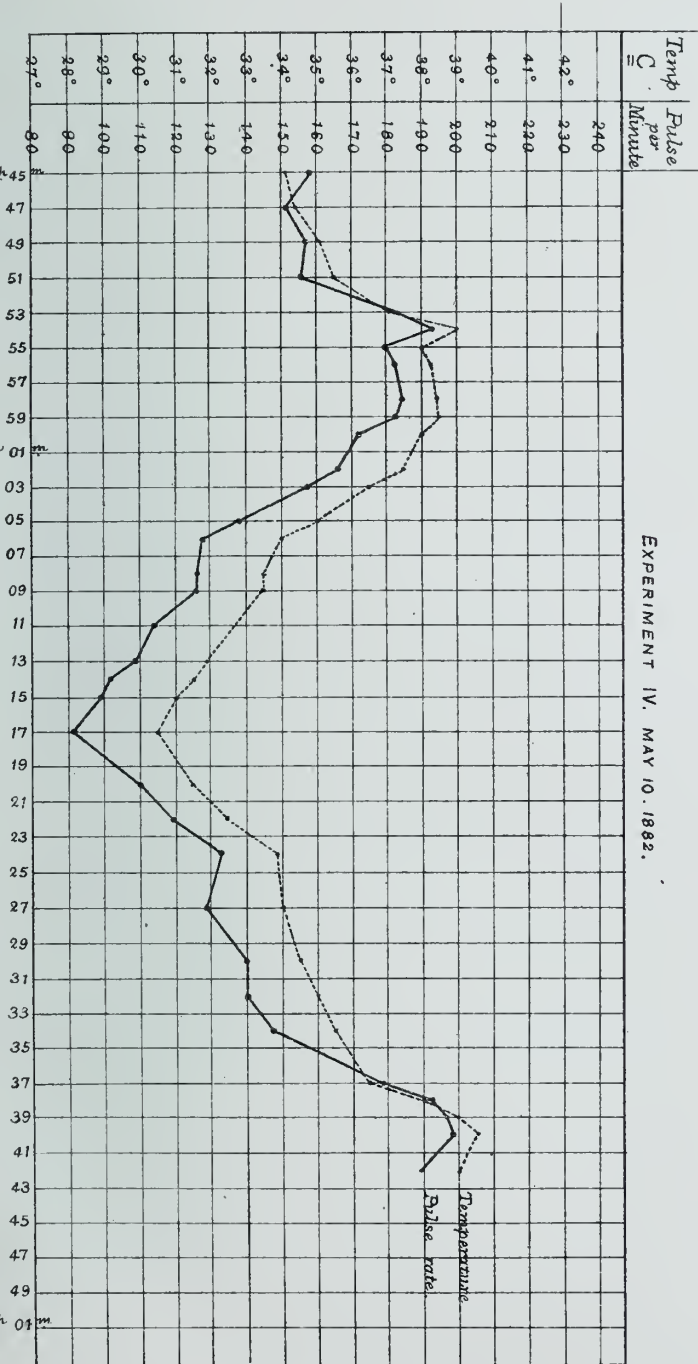
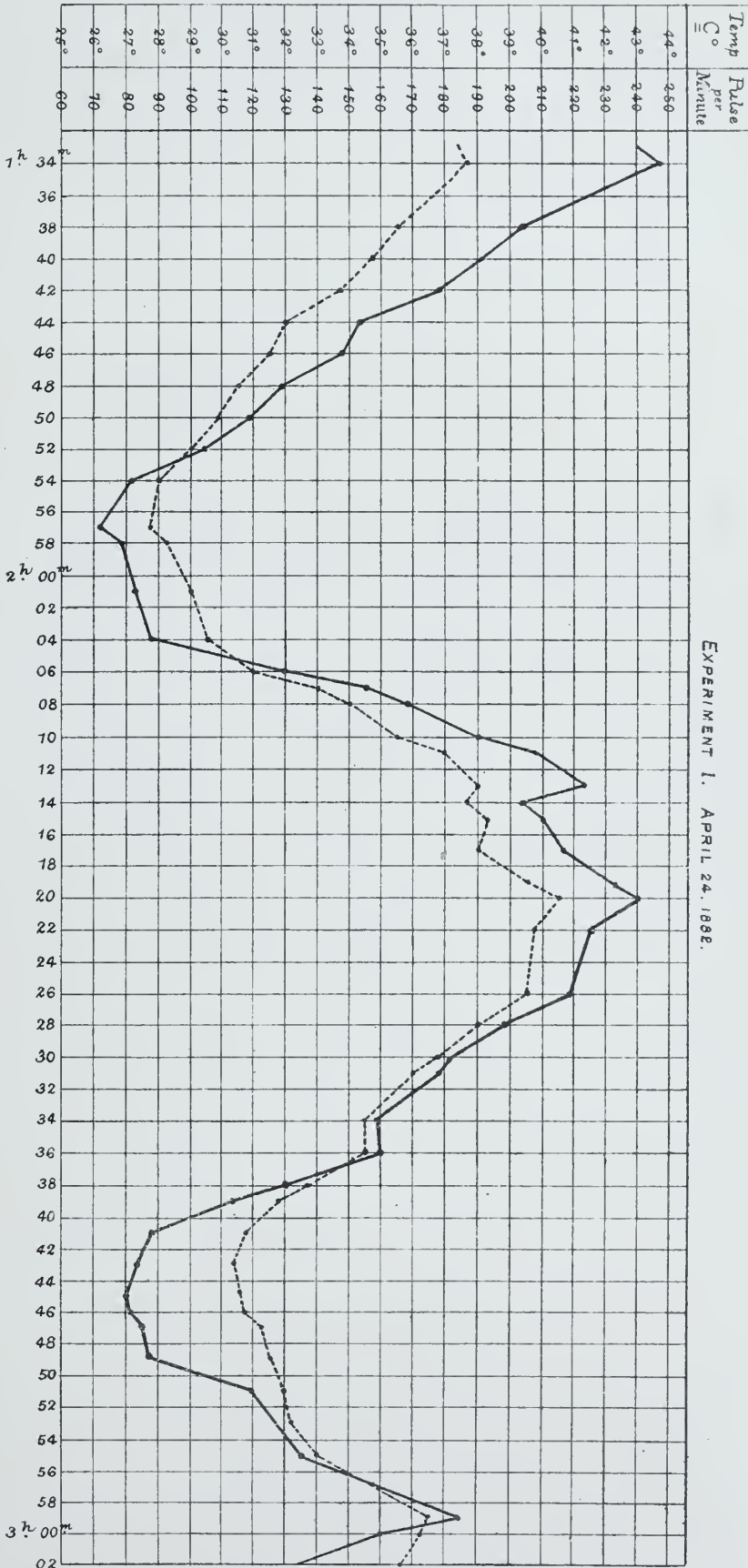


Fig. 1.





V.

THE ACTION OF ETHYL ALCOHOL UPON THE DOG'S HEART.

BY H. NEWELL MARTIN AND LEWIS T. STEVENS.

[*Studies from the Biological Laboratory of the Johns Hopkins University, Vol. II, p. 477, 1883. Transactions of the Medical and Chirurgical Faculty of Maryland, 1883, p. 216.*]

The physiological action of alcohol is a subject in connection with which very much has been written. In the Index Catalogue of the Library of the Surgeon-General's office there are more than one hundred and fifty separate references under the title "Alcohol, physiological effects of." From this vast mass of literature bearing on a subject which has been so often prominent in social and political discussions, very much may, of course, be at once eliminated as of no immediate interest to the physiologist or therapist in his capacity as such. It contains no original experiments, and is mainly a rhetorical and uncritical account of the work of others, often also described with a mental bias. After throwing aside these productions of the orators and essayists, there still remain numerous articles professing to deal with the physiological action of alcohol which can hardly be accepted as so doing, for in many cases all sorts of alcohol-containing drinks have been administered to men or the lower animals, and the results, if any, set down as due to the alcohol only. That this is not justifiable a moment's consideration will make clear, for it is well known that in different wines and spirits various substances are present which have potent action on the system, and cause these drinks, quite apart from the percentage of alcohol in them, to produce each its own characteristic effect, not only immediately after consumption, but, when taken in excess, remotely and permanently; as illustrated by the different pathological states to which they give rise or predispose. It is to this cause undoubtedly that the very discordant statements of various workers are mainly due: while there has also been a good deal of careless experimenting, such as the injection of large doses of 90 per cent. alcohol into the alimentary canal and the ascription of the consequences to absorbed alcohol, quite regardless of the intense local irritation which must have

been set up in the stomach or rectum of the animal experimented upon. During the last thirty years more careful work with reasonable doses and dilution, and with attention to the kind of alcoholic liquid used, has given better results. So far at least as the pulse is concerned, it seems fairly settled that alcohol diluted with water and in doses sufficient to produce transient disturbance of the mental faculties, has no effect on the pulse rate of healthy men or other mammals, though even here there is not absolute agreement. Zimmerberg,¹ whose paper is the most satisfactory of all those on the subject with which we are acquainted, found no pulse alteration caused by alcohol in dogs and cats when the animals were not tied down. Rabbits, on the contrary, showed a quickened pulse, but this seemed due to scare, for the same phenomenon was observed when a little water was injected into the animal's stomach. He also could discover no pulse quickening in man. Dr. Edward Smith,² however, found his own pulse quickened by alcohol, while that of Mr. Moul was unaffected. As Dr. Smith makes no statement as to whether he was accustomed to the daily use of alcohol, it seemed possible that he was an habitual abstainer, and that the pulse-quickening action of the alcohol in his case depended upon the fact that his system was quite unaccustomed to it. As this point seemed of interest and perhaps of practical importance, we asked a friend, aged about twenty-six, and who had never, so far as he knew, drank anything containing alcohol, to allow us to make an observation upon him. He kindly consented, and we give here the result before proceeding to the main series of our experiments. The alcohol used in this case and throughout our researches was that prepared by Squibb, and sold as "Absolute Alcohol" of sp. gr. 0.7850 at 25° C., and warranted to contain not less than 99.75 per cent. of pure ethyl alcohol. Mr. J.'s last meal was taken at 7 P. M. At 9 P. M. he lay down on a bed, and his pulse rate was noted at intervals for an hour. At 9 h. 05 m. it was 74 per minute, and varied between that and 71.5 until 9 h. 30 m.; he then became drowsy, and this and the recumbent posture brought the pulse down to 68 at 9 h. 58 m. At 10 h. 08 m. he was roused; at 10 h. 10 m. told he was to be given the alcohol. The substance really administered was, however, only some sugar and water—the object being to see what effect, if any, the idea of taking the drug (which might well excite a person accustomed to regard it somewhat in the light of a poison) would have on the pulse. There was a transient quickening to 73 per minute, but this was probably merely due to rising from the recumbent position in order to drink. At 10 h. 31 m. P. M., when the pulse had fallen to 70, 15 cub. cent. of

alcohol in 50 cub. cent. of water were given. This caused no rise of the rate of heart beat greater than two beats in a minute, and this only lasting a few minutes, and easily accounted for by the muscular effort involved in changing the posture. At 10 h. 52 m. the pulse was again 70 per minute, and thenceforth until the final counting, at 12 h. 10 m. A. M. its rate lay between 72 and 67 per minute—on the whole slowing towards the close of the experiment. This slowing can hardly have had any dependence on the alcohol, as it is well known that the pulse normally becomes less frequent towards midnight, and especially in a person who has lain for hours at rest. That the dose of alcohol was sufficiently large was evidenced by the dizziness produced by it.

We here give in tabular form the results of the experiment just described.

Hour.	Pulse rate per minute.	Notes.
P. M.		
9 h. 05'	74	Subject lay down on bed at 9 P. M.
" 15	75	
" 25	71.5	
" 27	73	
" 30	72.5	
" 42	67.5	Drowsy.
" 50	69	
" 58	68	
10 h. 08'	...	Aroused.
" 10	73	45 cc. of water with sugar in solution administered immediately before.
" 15	72	
" 25	71	
" 30	70	
" 31	...	15 cc. alcohol in 50 cc. of water given.
" 35	71	
" 40	70	
" 45	72	
" 52	70	Complains of slight dizziness.
11 h. 00'	67	
" 07	69	
" 19	68	
" 25	67	
" 35	68	
" 48	70	
12 h. 00'	68	
A. M.		
12 h. 10'	69	

Combining this experiment on a teetotaller with those of previous workers, we think it tolerably certain that moderate quantities of pure ethyl alcohol so diluted with water as to have no local irritant action, exert no influence on the pulse rate of healthy men. Possibly the con-

trary result obtained by Dr. Edward Smith is to be explained by the fact that he was experimenting upon himself. Although practised in so doing, he may not have always been able to suppress such an amount of interest in the result as amounted to a nervous excitement sufficient to influence his pulse. It is, perhaps, necessary here to definitely state that the above conclusion applies only to ethyl alcohol, and not to various wines and spirits. As regards several of these, the evidence collected by Dr. Edward Smith and others points the other way. Some quicken the pulse, and, so far as diseased persons are concerned, the clinical evidence seems conclusive that under certain conditions, some alcoholic liquids will remarkably diminish the rate of heart beat. In the treatment of the sick, however, pure diluted ethyl alcohol has rarely been used, and it may be that the influence observed on the pulse rate is a specific action of some of the other constituents of the liquids administered.

When a substance acts upon so many different systems of the body as alcohol does, it becomes no easy matter to get at its immediate specific action upon any one organ; yet a knowledge of this may be of primary importance. A given substance, for example, is known to raise arterial pressure; perhaps it is often a matter of no consequence whether it does this by increasing the heart's work or by constricting the arterioles; yet obviously circumstances may arise, *e. g.* a greatly weakened heart, when the administration of a drug constricting the arteries would perhaps temporarily increase arterial pressure, but in so doing throw so much extra work on the feeble heart as to lead to disastrous results. To raise therapeutics from empiricism or guesswork it is essential to know precisely the action of each drug on each organ in the body, and then its action upon them when working together in the living man. By the combination of careful observations at the bedside, with experiments made in physiological laboratories on the action of substances on healthy animals, and in laboratories of experimental therapeutics on healthy and diseased, we may hope in time to know, at least with tolerable exactness (for there will always be individual idiosyncrasies to be met and combated) exactly what any dose given to any patient is going to effect in him. The educated physician does not now prescribe as his predecessor would have done, a dose of salts for every case of constipation; he selects his purgative to suit the particular case and in accordance with his diagnosis of the seat of the trouble and his knowledge of the physiology of the alimentary organs and the specific action of the drug. To clearly establish for every substance used in medicine, first its special action upon

each organ when isolated, and then its action upon each organ when that organ is in vital connection with all the rest, is a task of almost appalling magnitude; but in proportion as it is accomplished will medicine become a trustworthy art based on scientific knowledge. Fortunately so much has been done of late years, especially in physiological and pharmacological laboratories, as to show that the task is not hopeless.

The investigation whose results are given in the following pages was undertaken with the hope of contributing some little to the attainment of the end above described, and also with the view of testing the availability of the dog's heart, isolated from all other organs of the body except the lungs, for therapeutical research. The latter subject seemed well worth investigating, as the hearts of frogs and reptiles, which have hitherto alone been experimented upon as regards the direct action of drugs upon the organ, differ in many fundamental points of anatomy, physiology, and nervous supply from the heart of man, while the dog's heart is practically identical with it in structure and working.

The animal having been narcotised by a large dose of acetate of morphia subcutaneously injected, or by the inhalation of the vapor of a mixture of ether and chloroform, the heart was isolated essentially in the manner described in a previous number of this journal (Vol. II, p. 213, Plate XV) [Plate 2 of this volume]. Certain modifications in the method, however, require mention.* Instead of allowing the right carotid to pump out through the tube *q* (Plate XV) [Plate 2 of this volume], and regulating the pressure in the aortic arch by opening the stopcock 22 more or less freely, the cannula inserted into the artery was attached to a long rubber tube which was led through the top of the warm chamber, in which the heart lay, to a height of several feet, where it ended in an outflow orifice. By varying the height of the point of outflow any desired arterial pressure could be easily obtained. We usually chose such a height as gave a mean pressure of 100 to 140 mm. of mercury, measured by a manometer connected with the left carotid, which recorded upon the paper of a kymograph, and thus also enabled us to count the pulse. We may at once dismiss the latter by saying that the doses of alcohol given by us had no effect upon its rate, thus confirming the results of the majority of recent observers.

In some cases the method was modified by tying up the right carotid instead of the aorta, and inserting into the latter a cannula of thin brass,

*The modifications here described are so inconsiderable and easily intelligible that it has not seemed to us necessary to illustrate them by a new plate.

as large as it would admit. This cannula was pushed up to the origin of the left subclavian and firmly tied there. To its distal end was connected a wide rubber tube, which led through the top of the warm chamber and ended in an outflow tube which could be raised or lowered at will. This modification was adopted to secure to the left ventricle a wide outflow channel, and thus eliminate a possible source of error due to its having only one carotid through which to empty itself. As will be seen subsequently, the result was the same whether the left ventricle had only the carotid through which to force its contents, or a tube of the full diameter of the thoracic aorta. This might perhaps have been expected, as the height to which the column of blood had to be pumped was, in both cases, arranged with reference to the diameter of the tube through which it was forced, so as to give about the same pressure in the aortic arch; in other words, to oppose the same resistance to the systole of the left ventricle.

The nutrient liquid sent to the heart was supplied from four Mariotte's bottles, either of which could at will be connected with the organ. One of these flasks, at the commencement of the experiment, contained two litres of fresh defibrinated dog's blood, mixed with 500 cub. cent. of 0.75 per cent. solution of sodium chloride in distilled water. At the commencement of an experiment this flask was put in connection with the superior vena cava, and supplied the right auricle under a pressure equal to that of a column of the blood mixture fifteen centimetres in height. This supply pressure was the same for all the four flasks, as they stood on the same level, and, as repeated trials showed, gave rise, when the cannula usually inserted into the superior cava was disconnected from that vessel and allowed to pour into a beaker, to a greater flow of blood than the left ventricle ever pumped out in an equal time; so that the heart always had opportunity to take up more blood than it accepted.

The blood received by the right auricle from the first Mariotte's bottle having passed through the lungs, was finally sent from the left ventricle through the outflow tube connected either with the right carotid or with the aorta. From the outflow tube it poured into a funnel from which it passed back into bottle No. 2, where it collected; this bottle being meanwhile in free communication with the atmosphere, but shut off from the heart. When No. 1 was nearly empty and No. 2 full, by turning a couple of stop-cocks, No. 2 was cut off from direct connection with the outer air and converted into a Mariotte's flask, and at the same time placed in communication with the superior cava. No. 1 was, simultaneously, cut off from

connection with the heart and arranged to receive the blood pumped out by the left ventricle and now supplied to the heart by No. 2.

One of us stood by the kymograph and looked after it; the other stood by the outflow tube. The former at intervals of a few minutes gave the word "get ready," and a few seconds afterwards "go." The other then immediately turned the outflow tube connected with the left ventricle so that it emptied into a beaker held in his hand. At the expiry of fifty-five seconds from the word "go" the warning "get ready" was again given, and at the end of a minute, upon a second utterance of the word "go," the collection in the beaker was stopped. The blood collected during this minute was measured and noted; and soon afterwards a new measurement of the quantity pumped out by the heart in a minute made in like manner. When bottle No. 2 was nearly empty and No. 1 full, the stopcocks were reversed and the heart fed from No. 1; and so on as often as necessary. The blood collected for measurement was poured back through the funnel into the bottle which happened to be the receiving one at the moment. When such measurements made five or six consecutive times agreed within a few cubic centimetres, the heart was considered fit for the examination of the action on it of alcohol-containing blood. Bottle No. 3 contained when the experiment commenced two litres of defibrinated dog's blood. As soon as it was ascertained that the heart was working with fair uniformity, 500 cub. cent. of 0.75 per cent. warmed sodium chloride solution to which alcohol had been added were mixed with the contents of No. 3. The quantity of alcohol used was such as to form either 0.25 or 0.5 per cent. of the whole; or, put in another way, 25 or 50 parts in 10,000. The total quantity of alcohol administered did not exceed in any case which we here record (larger quantities were given in other experiments with marked pathological results) 10 cubic centimetres, an amount contained in about $\frac{3}{8}$ oz. of good brandy. It must, however, be borne in mind that under the conditions of our experiments the only organs concerned were the lungs and heart, and that when alcohol is swallowed much of it may be held back in the liver or eliminated by the kidneys. It is therefore probable that much larger quantities of alcohol than those we employed might be administered by the mouth and absorbed and removed from the whole body without producing that influence upon the heart which our experiments demonstrate. When the alcohol-containing Mariotte's bottle was connected with the heart, the stopcocks were so turned that the blood pumped out flowed into bottle

No. 4; and while the heart was fed from No. 3, measurements of the blood pumped out in a minute were made in the manner above described. After the action of the alcohol had fully manifested itself, a bottle (No. 1 or 2) containing no alcohol was connected with the heart; if no marked recovery took place the experiment was rejected, as the diminished work might have been due to gradual death of the isolated heart, independent of any specific action upon it of the alcohol. When unmistakable recovery took place the experiment was recorded as a satisfactory one, even though the heart did not regain completely its original working power.

Care was of course taken to keep the blood supplied to the heart of as uniform a temperature as possible. Its temperature was observed by means of a thermometer inserted into the supply tube close to its attachment to the superior vena cava.

In a preliminary and general way our results may be stated as follows: *When defibrinated blood containing $\frac{1}{2}$ of one per cent. by volume of ethyl alcohol is supplied to an isolated dog's heart which has been hitherto working with uniformity, the invariable result is a very rapid and marked diminution in the work done (indicated by the quantity of the blood pumped out from the left ventricle) by the heart in a given time. When the blood contains only $\frac{1}{4}$ of one per cent. of alcohol the result is, in most cases, the same, but sometimes is little or none. After the action of the alcohol has been fully manifested the heart can in many cases be restored to its original working state if supplied with defibrinated blood containing no alcohol.* Blood containing but one-eighth of one per cent. of alcohol exerts no influence upon the work done by the heart, at least for several minutes.

As the heart was, under the conditions of the experiment, isolated from all extrinsic nervous control and supplied under exactly the same pressure with blood of exactly the same composition, except that one sample contained a little alcohol and the other did not, it was clear that in seeking an explanation of the above results we were limited to two directions: our apparatus might be imperfect, or the alcohol had a direct action upon the living organs, heart or lungs, or both.

As regards the apparatus, it was possible that the bottles filled with alcoholised blood flowed less freely than the others, and thus cutting off the supply to the heart, gave it less to pump out.

Repeated and most careful examination quite precluded this explanation. In many cases before commencing an experiment each of the four Mariotte's bottles was in turn connected with the vena cava cannula

and allowed to pour for a minute into a beaker, with the invariable result that the quantity collected from each one did not vary four per cent. from that obtained from any of the other three. We had in fact taken such care to have the connections and stopcocks of each bottle so similar that a different result could hardly have been possible. In other cases bottle 1 was first used to feed the heart; then alcoholised blood supplied from bottle 3, with the usual result. The heart was then recovered by good blood supplied from bottle 2, and meanwhile bottle 1 emptied of good blood and filled with alcoholised, its connections being left undisturbed. Then alcoholised blood from bottle 1 being supplied to the heart, we found invariably a marked diminution of work, although this bottle had previously, when filled with good (*i. e.* non-alcoholised) blood, kept the heart at full work; and it returned to this standard when subsequently supplied from bottle 3, which meanwhile had had its contents syphoned off and replaced with good blood. An absolutely incontrovertible proof that possible different rates of supply from the bottles had nothing to do with the general result will appear later when we describe the effect of removal of the pericardium.

Once defects of the apparatus were eliminated we had to seek the cause of the result obtained in the heart or lungs. It seemed conceivable (*a*) that the alcoholised blood constricted the pulmonary vessels or otherwise impeded the flow from right ventricle to left auricle; or (*b*) that it greatly dilated the coronary vessels of the heart and allowed so much blood to be diverted through them as to seriously diminish the proportion of the total amount pumped into the root of the aorta, which was left over to be pumped through the carotid or aortic cannula, with which our outflow tube was connected; or (*c*) the alcoholised blood might act injuriously on the ganglia and nerves of the heart; or (*d*) it might act injuriously upon the cardiac muscular tissue.

We were quite at a loss for a time in endeavoring to decide between the above possibilities. At last it was observed that when the heart was supplied with alcoholised blood and this diminished the work done, the organ invariably was much distended, closely filling the pericardiac sac. In the latter a minute hole was always cut as soon as the heart was placed in the warm chamber, to prevent the accumulation of lymph within it, which otherwise is apt to occur; probably because the efferent lymphatic trunks have been tied or twisted in the operations of isolating the heart and inserting the cannulas. After noticing the expansion of the heart above mentioned, our next experiment was modified by cutting

away the pericardium before any observations were made. We then found that even blood containing $\frac{1}{2}$ of one per cent. of alcohol, which had never previously failed to cause a marked diminution in the heart's work, was almost without effect on it. In other cases the experiment was modified by first leaving the pericardium intact and getting the usual alcohol result; next, recovering the heart by supplying it with good blood; then cutting away the pericardium and supplying alcoholised blood from the same flask as before. This now had no effect on the work done by the heart in a minute; though, as will be more precisely stated later, it had a noticeable influence on the bulk of the heart.

Removing the pericardium could obviously have no influence on the rate of supply from our bottles or on the calibre of the pulmonary arterioles; so those possible causes of the general result of the alcohol administration were definitely set aside. It also seemed hardly conceivable that dilatation of the coronary vessels caused the less outflow from the carotid artery or thoracic aorta; for compression of a distended heart by its surrounding pericardium would oppose such dilatation, and the effect ought therefore to be most marked after the removal of that sac, which was exactly the reverse of what we found to occur. That the contractile force of the heart was not directly affected seemed also demonstrated by the very slight diminution of work, if any, which occurred on the administration of alcohol after removal of the pericardium. We thus seemed driven to seek for some alteration in the physical condition of the organ which impeded its action and diminished its work. This alteration was not far to seek. The great swelling of the heart when under the influence of alcohol was obvious. At the height of each systole it nearly filled the pericardiac cavity, and during the diastoles had little opportunity to dilate and receive a fresh supply of blood. Hence the quantity pumped out at each beat became less and less in proportion as the heart swelled. As it seems tolerably certain that the normal heart beat is of such character that, at the end of each systole, the ventricular cavities are entirely emptied and obliterated, we may state our results as follows: *The action of alcohol administered in the manner and doses above described, is, without primarily altering the force of heart beat, to alter its character, so that the ventricular cavity is not obliterated at the end of systole, and less so the longer the alcohol has been administered. At first this incomplete systole is compensated for by a more extensive diastole, so that the difference between the capacity of the ventricle in complete diastole and that in complete systole remains the same as when the organ was normally beating. Consequently, the*

quantity of blood pumped out at each beat remains as great as before. If the heart be confined in the pericardium it soon, however, ceases to have room to swell during diastole to a size sufficient to compensate for its incomplete systole; and thenceforth, as the swelling increases, the difference between diastolic and systolic capacity becomes less and less. As the necessary result, the quantity of blood pumped round by the organ is proportionately diminished. Removal of the pericardium prevents this result, at least for a considerable time.

Probably the diastolic increase would ultimately, even with the pericardium removed, gain a maximum before the systolic increase of ventricular capacity had reached its limit, if alcohol were administered a longer time, and there would then be a diminution in the blood pumped round; but upon this point we are not prepared at present to make a positive statement. When hearts freed from the pericardium showed a distinct diminution in the work done, we have never been able to obtain any satisfactory recovery; and as above stated, we are unwilling to lay stress on experiments in which no such recovery was obtained when good blood was substituted for alcoholised.

Gaskell has shown³ that the heart of the frog and toad can have the extent of its systole or diastole controlled by the vagus nerve. Hence it may be that the characteristic physical change wrought in the muscle of the dog's heart by alcohol is indirectly produced by a primary action of the drug on vagus nerve endings in the organ. Gaskell, himself, however,⁴ and Roy,⁵ Ringer⁶ and others, have found that various substances supplied to the apex of the frog's ventricle bring about a condition of imperfect systole similar to that which we find produced in the dog's heart by alcohol; while other substances exert the reverse effect, bringing the frog's apex into an almost tetanic state of systole. Hence, reasoning from analogy, it is also possible that the alcohol acted directly upon the cardiac muscle. At present we do not find ourselves in a position to decide between these possibilities.*

The therapeutical significance, if any, of the results obtained by us we do not feel qualified to discuss; but we may point out that our work

*This paper was read before the Medical and Chirurgical Faculty of Maryland on April 27, 1883, and an abstract of it published in the *Medical News*, Philadelphia, May 5, 1883. Since the present article was put in type, a paper by Ringer and Sainsbury has appeared in the *Practitioner* for June, 1883. They experimented with various alcohols on the frog's ventricle, and found all stopped the heart in diastole. Their work makes it probable that our results are due to direct action of the ethyl alcohol on the muscular tissue of the dog's heart.

seems to show that alcohol should be used with caution in cases of pericardiac effusion, where any increase in the size of the organ, hampered as it is already by the liquid around it, could only be harmful. We trust shortly to investigate the action of other substances upon the isolated dog's heart; especially those substances which have been found to produce dilatation or contraction in the hearts of amphibia and reptiles. If we can establish for the mammal the results which others have obtained on the lower vertebrates, we may perhaps add some little to the knowledge available to the physician in his treatment of the pathological conditions known as dilated and contracted heart.

We append in tabular form the details of some of our experiments. The only point which we think may need explanation is the fact that in some cases arterial pressure is seen to fall while the heart was still pumping some blood up to and out of the outflow orifice, which was maintained at a uniform height. This is due to the fact that the pressure recorded by the manometer depended on two factors: one (the main one), the height of the exit of the outflow tube above the level of the heart; the other, an elastic reaction of the aortic arch and the arterial stumps connected with it, and of the elastic rubber outflow tube, due to the fact that when in good working condition the heart kept them all slightly on the stretch. When the heart pumped less blood this tension diminished or disappeared, and the pressure in the stump of the carotid with which the manometer was connected fell accordingly.

The numbers in the column headed "outflow" give the number of cubic centimetres of blood pumped by the heart through the outflow tube in the minute ending at the time stated in the first column. The figures in the column headed "pressure" indicate millimetres of mercury.

March 12, 1883. Animal under the influence of morphia during the preliminary operation. Heart isolated at 2 h. 05 m. P. M. Outflow through right carotid. Pressure measured in left carotid.

Time—P. M.	Pressure.	Outflow.	Notes.
2 h. 23'	140	198	
" 28	138	193	
" 30	140	197	
" 36	139	188	
" 42	141	199	
" 47	140	190	
2 h. 47' 30"			Alcoholised blood, 0.25 per cent., turned on.
" 49	125	118	
" 51	122	97	
" 54	120	96	
" 56	124	103	
2 h. 56' 15"			Good blood turned on instead of alcoholised.
3 h. 01'	135	142	
" 06	134	148	Marked recovery.
3 h. 14' 00"			Pericardium cut away.
" 21	133	166	
" 29	140	205	
" 33	142	203	
" 36	142	199	
3 h. 37' 30"			0.25 per cent. of alcoholised blood turned on.
" 41	135	169	
" 43	133	161	Pulse slightly irregular.
3 h. 43' 15"			Good blood turned on.
" 47	135	168	
" 53	134	168	The heart now became very irregular and was obviously dying. The experiment, however, shows well enough the comparatively slight action of the alcohol after the removal of the pericardium.

April 26, 1883. Very small dog; under morphia while heart was being isolated. Heart isolated at 2 h. 03 m. P. M. Outflow cannula in aorta. Pressure measured in left carotid.

Time—P. M.	Pressure.	Outflow.	Notes.
2 h. 21' 00"	99	140	
" 23	99	142	
" 25	99	140	
" 27	99	145	
" 30	99	145	
2 h. 31' 00"			0.25 per cent. alcoholised blood turned on.
" 33	98	121	
" 35	98	116	
" 38	98	100	
" 41	98	98	
" 44	98.5	100	
2 h. 44' 20"			Good blood turned on.
" 46	99	129	
" 50	98.5	125	
" 52	98.5	123	
" 55	99	122	
" 57	99	120	
" 59	98	126	
3 h. 00' 00"			0.5 per cent. alcoholised blood turned on.
" 02	96	60	
" 04	96	28	
" 06	95	8	
" 10		0	Pressure rapidly falling as the blood sank in the outflow tube; not enough being pumped out by the left ventricle to supply the coronary arteries.
3 h. 10' 15"			Good blood turned on; the exact moment of turning on the good blood has unfortunately been omitted in the record of the experiment. It was probably at the time here stated, but may have been just before 3 h. 09'.
" 11			A few drops of blood pumped out of the outflow orifice.
" 13	98	100	
" 15	98.5	121	
" 17	98	116	
3 h. 19' 00"			Pericardium cut away.
" 22	98	135	
" 24	98	135	
3 h. 24' 45"			Alcoholised blood (0.5 per cent.) turned on.
" 26	98	133	
" 28	97.5	120	
" 31	97.5	110	Heart greatly swollen.
" 33		103	
" 35	97	105	
3 h. 35' 15"			Good blood turned on.
" 37		137	
" 39		127	
" 41		128	This experiment shows well the much greater effect produced by the blood containing one-half of one per cent. of alcohol than that containing one-quarter. Also the much less effect of the alcohol in so far as quantity of blood pumped around is concerned, after removal of the pericardium.

May 31st, 1883. Medium sized dog, etherised while the heart was being isolated. Heart isolated at 3 h. 55 m. P. M. Outflow cannula in aorta. Pressure measured in left carotid.

Time.	Pressure.	Outflow.	Notes.
4 h. 20' 00"	102.5	283	
" 26	103	285	
" 28	103	273	
" 30	103	279	
4 h. 30' 30"			0.5 per cent. alcoholised blood turned on.
" 32	100	198	
" 34	98	109	Heart much distended.
" 36	97	88	
" 38	96.5	63	The pulse waves on the kymograph tracing have become very feeble.
4 h. 38' 20"			Good blood turned on.
" 40	98	98	
" 42	102.5	264	
" 44	102	266	
" 46	102.5	270	
4 h. 48' 00"			A large slit cut in pericardium.
" 50	103	283	
" 53	103	281	
" 55	102	278	
" 57	102	277	
4 h. 57' 45"			0.5 per cent. alcoholised blood turned on.
" 59	98	180	
5 h. 01' 00"	99	175	The pericardium was now completely removed, as it was observed that although the ventricles projected through the opening made in it, the auricles, especially the right, were compressed and impeded in their diastole.
" 05	101	260	
" 07	100.5	245	
" 09	100	241	
5 h. 12' 30"			Good blood turned on.
" 15	103	295	
" 17	102.5	278	
" 19	102.5	284	The experiment was stopped here, with the heart and lungs still in good condition. On the whole, it is one of the most satisfactory in our series, as the lungs remained in good order throughout, instead of becoming oedematous towards the end of the experiment, as they usually do, impeding the blood flow and more or less vitiating the result. This gradually increasing pulmonary oedema is one reason why we have rejected all experiments but those in which the heart showed decided recovery after the removal of the alcoholised blood; it is, also, we feel sure, mainly responsible for our failure in most cases to get a complete recovery of the organ as indicated by the outflow.

February 26th, 1883. Animal under morphia while heart was being isolated. Isolation completed at 1 h. 05 m. P. M. Outflow cannula in right carotid. Pressure measured in left carotid.

Time—P. M.	Pressure.	Outflow.	Notes.
1 h. 42' 00"	122	204	Pericardium removed before the first measurement of outflow was made.
" 45	121	202	
" 48	123	207	
1 h. 50' 00"			0.25 per cent. alcoholised blood turned on.
" 52	119	200	
" 54	117	184	
" 56	117.5	183	Good blood turned on.
1 h. 57' 00"			
" 59	116	183	
2 h. 13' 00"	122	198	Three measurements made between 1 h. 59' and 2 h. 13' were thrown aside as useless, on account of the discovery of a bubble of gas imprisoned in a bend of the supply tube of the Mariotte's bottle. This greatly diminished the quantity of blood reaching the heart. Another bottle having been connected with the heart, the gas was removed and the experiments continued.
" 16	122	203	
" 21	122	200	
" 26	119	202	
2 h. 27' 00"			
" 29	118	197	0.25 per cent. alcoholised blood turned on.
" 32	120	198	
2 h. 33' 00"			Good blood turned on.
" 36	126	210	
2 h. 38' 00"			0.5 per cent. alcoholised blood turned on.
" 40	120	202	
" 42	123	205	
" 45	122	205	
2 h. 46' 00"			Good blood turned on.
" 50	123	200	
2 h. 51' 00"			1 per cent. alcoholised blood turned on.
" 53	119	195	
" 55	117	192	
" 57	117	190	
" 59	118	191	
3 h. 00' 00"			Good blood turned on.
" 03	121	203	
" 07	123	208	
			Throughout this experiment the lungs kept in good condition. It shows very well the slight effect of alcohol on the quantity of blood pumped out by the heart when the pericardium has been removed. Even blood containing 1 per cent. of alcohol had very little influence in diminishing the outflow.

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VI.

EXPERIMENTS IN REGARD TO THE SUPPOSED "SUCTION PUMP" ACTION OF THE MAMMALIAN HEART.

BY H. NEWELL MARTIN AND F. DONALDSON, JR.

With Plate 5.

[*Studies from the Biological Laboratory of the Johns Hopkins University,*
Vol. IV, p. 37, 1887.]

That the heart acts not only as a force pump during its systole, but during its diastole actively expands and thus gives rise to a negative pressure, which causes blood to move from the systemic veins to the right auricle, has long been maintained. Indeed, while the thorax and lungs are intact there must undoubtedly be some such "suction" action; the elastic reaction of the lungs pulling on the heart must expand it when its walls are relaxed and flabby in diastole. The heart during its systole does extra work in overcoming pulmonary elasticity (as evidenced by the negative pressure then observable in the lungs*), and during diastole gets this work returned to it as a distending force.

But the question still remains whether, after the thoracic cavity has been opened, the heart expands in diastole passively in consequence of the positive pressure exerted by blood driven into it from the veins, or actively, and in the latter case, by causing a negative pressure, causes blood to flow towards itself, even when there is no positive pressure in the *venæ cavæ*? Fick,† nearly forty years ago, showed that the hearts of oxen, sheep and men, when in *rigor mortis*, actively expanded after compression; but he also demonstrated that perfectly fresh excised hearts had no such tendency: they only expanded and received liquid from outside when it was sent into them under positive pressure.

It was, however, conceivable that the heart in the living body, with blood flowing through the coronary arteries and capillaries and veins, might behave differently. If we imagine the relaxed heart as a bag with

* Voit, *Zeitsch. f. Biol.* I, p. 390; Klemensiewicz, *Mitt. d. Ver. d. Aerzte in Steiermark*, 1875-76, p. 41: and others.

† Müller's *Archiv*, 1849, p. 283.

very soft and distensible walls, it is easy to see that a network of distended elastic tubes ramifying in its substance might cause active expansion of its walls and dilatation of its cavities. Starting from this theory, Thebesius and, independently, many years afterwards Brücke, suggested the doctrine of the "*selbst-steuerung*" of the heart. According to this doctrine, the aortic semilunar valves press close against the walls of the vessel during ventricular systole, and cut off the blood-flow to the coronary arteries; these arteries therefore become comparatively flaccid; but during diastole the valves flap back, and blood rushing into the coronaries distends them, and through them the walls of the heart, in which they ramify.

The "*selbst-steuerung*" doctrine in its fullest sense may now be considered as disproved, many facts quite inconsistent with its truth having been demonstrated.

But, although the belief that the mouths of the coronaries are closed during ventricular systole was no longer tenable, it was still possible that the distended elastic arterial branches ramifying in the myocardium should mechanically tend to stretch the walls and dilate the cavities of the heart. During systole the muscular force would easily overcome this stretching tendency of the tense vascular network; but during diastole it is easily conceivable that the muscle might yield in turn and the heart cavities be actively distended. It was to put this question to the test of experiment that the research described in this paper was undertaken. We wished to ascertain whether, at any period of the heart's beat after the thorax had been opened, a negative pressure existed in the right auricle.

The negative pressure proved by Goltz and Gaule to occur in the ventricles for a brief period at the end of the systole, had already been shown by Moens* not to affect the auricles, and therefore to be without effect in making the heart a suction pump so far as the venous system was concerned.

The general plan on which we worked was to open the thorax, maintaining artificial respiration and leaving the lungs and the pulmonary blood-flow intact. Then, to place a long tube in the aorta just beyond its arch, and occlude all the branches leading from the aorta except the coronaries. Also, to close the great systemic veins near the heart, except one, which was in connection with a reservoir containing defibrinated blood. This reservoir was connected with the outflow tube tied into the

* Pfüger's Archiv, XX, p. 517.

aorta. Thus the whole systemic circulation was represented by the coronary system and a set of rubber tubes which started from the aorta and returned to the right auricle. The heart and lungs being freely supplied with blood, long retained their vitality, and the heart, as we knew by previous work, could in this manner be kept beating normally and vigorously for hours. Then, by connecting a manometer tube filled with blood, to the side of the cannula leading to the right auricle, and cutting off all blood-supply to the right heart except from this manometer tube, we could easily ascertain whether the right heart exerted a negative pressure, so as to be able, in common phraseology, to "suck" blood out of the manometer after the level of the blood in it was below the level of the right auricle.

The method of experiment was in essential features that described by one of us* four years ago. As it has not yet been given in detail in any journal published in the United States, it may be well to here repeat the description, embodying in it such minor changes in the apparatus as have been made since 1883, and a description of the manometer tube and its connections as specially added for the present research.

Small dogs were used; in the present series of experiments they were always deeply narcotized by the subcutaneous administration of sulphate of morphia before the operation was begun. Then tracheotomy was performed, the external jugular vein exposed on one side of the neck, and sufficient curare solution injected into it to prevent reflex muscular contractions. Artificial respiration, maintained uniformly by a small water engine, was started as soon as the curare began to influence the movements of the respiratory muscles.

The further course of the operation was as follows: The pneumo-gastro-sympathetic trunks were divided on each side of the neck, a cannula put in the right common carotid, and the left ligated. Next, the first pair of costal cartilages and the bit of sternum connected with them were removed, along with the episternum; then the internal mammary arteries were tied on their course from the subclavians to the breast-bone. The skin and other tissues covering sternum and costal cartilages were next removed, and the breast-bone and rib cartilages cut away, back to the diaphragm. Then most of the right side of the thorax was removed, any intercostal arteries which spirted being twisted or pinched. The right subclavian artery was prepared, and ligated where it separated

* H. Newell Martin : Direct influence of gradual variations of temperature upon the rate of beat of the dog's heart. Phil. Trans. Roy. Soc. Pt. II, 1883.

from the carotid. The superior vena cava was cleaned, and two ligatures placed loosely around it, to be used subsequently. The right azygos vein was ligated close to its entry into the superior cava, and a ligature was placed loosely around the inferior cava just above the diaphragm.

Proceeding now to the left side of the chest, the subclavian artery was ligated, and the left lung being gently held aside, the aorta isolated and cleared near the diaphragm. A ligature was placed loosely around this vessel just beyond its arch, and a strong clamp tightened on it to the distal side of this ligature. An aperture having been made in the thoracic aorta near its posterior end, a cannula, filled with defibrinated blood, was inserted into the vessel, and the aortic clamp being removed, was pushed up to the left end of the aortic arch, where the ligature above-mentioned was tied tightly around it. [These aortic cannulas are made of thin brass tubing, and are kept at hand of several sizes, so that one can always be found which fits tightly into the aorta of the animal, and is closely clasped by the elastic walls of that vessel. The cannula has on its distal end a piece of rubber tubing on which is a clamp, which is screwed tight when the tube is filled with defibrinated blood before its insertion into the artery.] The ligature around the inferior vena cava was next tightened, and a cannula filled with defibrinated blood inserted as quickly as possible into the superior cava and tied in place. This cannula was at once connected with *y*, Pl. V [Plate 5 of this volume], Fig. 1.

So far all the systemic arteries but the coronaries of the heart had been occluded. One common carotid had a cannula in it, and the other was ligatured; both subclavians were ligated below the point at which they gave off any branch, and the aortic cannula was tied in at a level of the vessel, just beyond its arch, at which it had given off no bronchial or intercostal branches.*

The animal was now transferred as quickly as possible to the warm moist chamber, which, with its contents and accessory parts, we have now to describe. It is represented, semi-diagrammatically, in Pl. V [Plate 5 of this volume], and is 125 centim. in length, 65 centim. in width, and for the greater part of its length is 65 centim. in height. At one end, however, *E*, its height is 130 centim. It has no bottom, but when in use sits

* Sometimes in young dogs a minute branch is given off from the innominate artery to the thymus. This was sometimes tied, but usually neglected, as it is difficult to get at, the amount of blood drained off by it is trivial, and when both venæ cavæ are tied, cannot get back to the heart. The large thymus in puppies makes the operative part of the experiment more difficult in them, but not to any important degree.

in a shallow iron trough (not represented in the figure) filled with water, and raised on supports which admit of Bunsen burners being placed under it; by their means the air in the chest is kept moist and warm. The roof, sides, and one end are glazed; the end, *B*, *E*, is of wood, and perforated by apertures through which several tubes pass. The object of glazing most of the walls of the chamber is to enable a ready view to be had of what is going on inside it; this is apt to be interfered with by condensation of water on the glass during the course of experiment; this drawback may, however, be nearly entirely obviated by smearing the inside of the glass with glycerine. One side of the warm chamber, that turned towards the observer in Pl. V [Plate 5 of this volume], Fig. 1, is so arranged as to be readily removed and replaced. In it are also several doors which can be opened or closed without removing the whole side of the chamber. These are not represented in the plate. In the chamber are two Mariotte's flasks, *C* and *D*, each of the capacity of two litres. The flasks are entirely similar in all respects, but are so arranged and connected that, at will, either one can in a moment be made to supply blood to the heart or receive blood from it, and always under a constant or any selected pressure, and without opening the warm chamber.

Let us take the flask *C* for more detailed description. Its neck is closed airtight by a rubber stopper through which four glass tubes pass. Two of these tubes, *c* and *d*, end a short way below the stopper, and are open to the exterior when the flask is receiving blood. By means of the rubber tubing *l'*, Fig. 1, *c* is connected with the three-way stopcock *X*, Fig. 2, and beyond it, by *l* with the funnels *r* and *x*. From these funnels the flask is supplied with blood. The tube *d*, with its rubber extension, leads to the stopcock *g*, Fig. 2; it, when open, permits the escape of air when blood enters *C* from either of the funnels.

The two remaining glass tubes, *e* and *f*, reach nearly to the bottom of the flask; they are kept closed when *C* is receiving blood, but are opened when it is supplying blood to the heart. Of the two, *f* reaches about half an inch lower than *e*; it is connected by *k* (Figs. 1 and 2) with the three-way cock *W*. From the cock leads the tube *n*, which re-enters the warm chamber, and is connected, during an experiment, with the superior vena cava by the intervention of *o*, *q* and *y*. It serves to supply the heart with blood.

The tube *e* is connected with the stopcock *u*. Through it air enters the flask *C* when it is sending blood to the heart.

The tubes connected with the flask *D* are in all respects similar to those opening into *C*, *c'* answering to *c*, *d'* to *d*, *e'* to *e* and *f'* to *f*, and so

forth. The stopcock *X* is so arranged that when the passage from *c* is open that to *c'* is closed, and *W* so that when the passage from *f'* is open that from *f* is shut.

The flasks are represented as resting on the block *S*, in order to avoid more complication in the figure. In reality they stand on a movable platform which can be raised or lowered; and before using they are raised until the bottom of each is about twelve centimetres above the level of *y*, which itself is about 40 centimetres above the bottom of the water trough on which the warm chamber rests.

Before an experiment the flask *C* is nearly filled with defibrinated blood, and *D* about one-fourth filled. This is done from the funnel *r* by opening and closing the proper passages or stopcocks.

The next step is to fill the tube *f* and its fellow, and all the passages connecting them to *y*, with blood from the flasks. These tubes have alternately, during the experiment, to act as syphons, supplying the heart. To fill them, *X*, Fig. 2, is so turned as to close *l'*, and of course *c*, to which it leads; *g* is turned so as to cut off *d* from communication with the air; *W* is turned so as to open a free passage from *f* through *k* to *n* and thence through *o* and *q* to *y*. Also, *u* is opened so as to place *e* in free communication with the atmosphere. Suction is then applied to *y*, the stopcock *q* being open. Air then enters *C* through *e*, and blood passes out to *y* through *f*, expelling the air previously in the connecting tubes between *f* and *y*. As soon as all the air is expelled the stopcock *q* is shut. *C* is now a Mariotte's flask; on opening *q* it will deliver blood in an even flow and under uniform pressure at *y*, the flask having of course been previously raised so that the lower end of *f* is higher than *y*.

When the tubes connecting *C* with *y* are full, the stopcocks *X* and *W* are reversed; *g* is opened, *u* closed; and *g'* closed and *u'* opened. Then, on *q* being opened and suction again applied at *y*, the tubes leading from *D* to *y* are filled with blood, so that *D* shall act as a Mariotte's flask. Then *q* is closed, *g'* opened and *u'* shut.

The warm chamber is now closed; the stopcocks *X* and *W* again reversed, so that the fuller flask *C* shall be in connection with *y*. But *g* is left open, so that as the blood and air in the flask expand while they heat, air may escape. From time to time *g* is closed and *q* opened; a few centimetres of blood are collected in a beaker and the temperature of the blood noted. This temperature is indicated by the thermometer *p*, the bulb of which reaches into the enlargement *o*. The blood collected is returned to *D* by pouring it into the funnel *r*.

Meanwhile, the preliminary operation on the dog was carried on up to the point of opening the thorax. As soon as the temperature of the blood reached about 38°C ., the gas flame under the warm chamber was turned low and the operation on the animal completed, as already described. Then the dog was immediately transferred to the warm chamber, and the cannula in its superior cava connected with *y*. At the same moment *g* was closed so that *C* should act as a Mariotte's flask; then *g* was opened and blood allowed to flow into the right auricle of the heart, under a constant pressure equal to about that of a column of blood ten centimetres in height. The clamp on the rubber tube of the aortic cannula was loosened and the heart allowed to pump out blood in a free stream, but still not so free but that considerable arterial pressure was maintained in the aortic stump, and, from it, in the coronary arteries of the heart. After a minute or so, when it was judged that all the blood previously contained in the isolated heart and lungs had been washed out and replaced by defibrinated blood, the rubber tubing on the end of the aortic cannula was quickly slipped over *h* and the clamp on this tubing removed. The heart then pumped blood up through the tube *t* to the funnel *x*, and from the funnel the blood returned by *l* and its side branch *l''* to *D*. Thus as *C* emptied, *D* filled. When *C* was nearly empty and *D* nearly full, it was easy, by reversing the stopcocks *X* and *W* and opening or closing *g* or *g'* and *u* or *u'*, as the case might be, to make *D* the supplying flask and *C* the recipient. Thus the same blood could be circulated again and again through the heart and lungs, and always be supplied from the superior cava uniformly to the right auricle, while aortic pressure could be kept constant; or, if desired, varied within wide limits by raising or lowering the level of the funnel *x*.

Finally, the cannula in the right carotid having been connected with a mercury manometer, which recorded arterial pressure and the pulse rate on the paper of the kymographion, the front of the warm chamber was replaced.

Of course, artificial respiration was maintained throughout the experiment. The air-supply tube from the respiration pump leads to a three-way stopcock; one branch of the stopcock opens into a tube which leads to the operating table; the other branch into a tube which leads into the warm chamber. As soon as the animal is removed from the table to the chamber, the stopcock is turned so that the air blast enters the tube leading to the warm chamber, and this is immediately connected with the cannula in the trachea.

By means of the thermometer *p* the temperature of the blood supplied to the heart can be ascertained; this can be kept fairly uniform by raising or lowering the flames of the Bunsen burners beneath the warm chamber, as desirable. We also found it useful to surround with raw cotton the parts of the tubes *t* and *l* which lie outside of the chamber. By surrounding *C* and *D* with water jackets* the blood supplied to the heart can be kept at an almost uniform temperature. But as such uniformity was not necessary in regard to the experiments to be described in the present paper, the water jackets were not used. The blood was in every instance kept near 38° C., and never varied more than 2° C. from that temperature during the time in which our observations were made.

It still remains to describe that part of the apparatus, viz. *abm*, which was specially devised for the series of experiments to be described in this paper. Between *q* and *y* is intercalated the top of a T-piece; on the leg of this T-piece is the stopcock *a*. When this is closed, all blood passing *q* must take its course to the heart through *y*; but if *a* be opened, some of the blood will flow into the U-tube *bm*, which is fixed at such a level, after the animal has been put in the warm chamber, that the upper end of the open limb *m* is above the level of the right auricle of the heart. The limb *b* can be opened or closed at will by the stopcock *s*.

So soon as the heart was ascertained to be pumping blood round well and uniformly, *a* and *s* were partly opened and a portion of the blood-supply diverted until the U-tube was filled to near the top of *m*. Then the stopcocks were closed, and all the blood again flowed through the heart. Next, the height of the point of entry of the superior cava into the right auricle was carefully measured from the bottom of the warm chamber. This was done by placing the lower edge of one end of a spirit-level on the cannula connected with *y*, and close to the heart. After getting the level perfectly horizontal, the distance of its lower edge from the bottom of the trough was measured. This gave the height above the bottom of the trough of the upper side of superior cava where it joined the auricle.

If now *q* be closed and *a* opened, the right heart no longer can get blood from the Mariotte's flask. Its only source of supply is from the previously filled U-piece. If it takes blood from this until the level of the liquid in *m* falls below the level at which the vena cava enters the auricle, then the right heart has exerted some suction, it has actively expanded; while if it only continues to supply itself so long as the level of the blood in *m* is higher than the level of the entrance to the auricle, it is clear that the heart only takes blood when supplied to it under some positive pres-

* Phil. Trans. Roy. Soc. Lond., Pt. II, 1883.

sure, and that it is not a suction pump. So soon as the level of the blood in *m* ceased to fall, its height from the floor of the trough was measured and noted. Then *q* was opened, and the heart thus again is supplied with blood from one of the Mariotte's flasks, while the U-tube *bm* was also refilled. Then *a* was closed. After waiting a minute or two, *q* was once more closed and *a* opened, and the observation repeated; and so on as often as might be desired, or until the heart began to show symptoms of weakening.

We made in all nine experiments as to the capacity of the right heart to actively take blood from the superior cava after the thorax had been opened; and in the course of each experiment the conditions were varied. At the commencement arterial pressure was medium (about 95 mm. Hg), and the pericardium was intact. Then arterial pressure was varied within wide limits, by raising or lowering the level at which *t* emptied into *x*. Moderate and violent artificial inflation of the lungs were employed, and also the entire cessation of the artificial respiration. Finally, in order to give the heart the greatest possible freedom, the pericardium was cut away, and the observations repeated. But in no single case did we find that the right auricle would receive blood unless that blood were supplied to it under positive pressure, the minimum pressure required varying little from that exerted by a column of blood about 12 mm. in height. It might fall to 8 mm. or rise to 18 mm., but those were the limits.

The earlier experiments were made with the defibrinated blood of young sucking calves. Though the isolated heart of the dog will work well for hours when supplied with this blood, it was possible that it might injuriously affect the elasticity of the heart muscle, so our final experiments were made with the hearts of dogs supplied with defibrinated dog's blood, obtained by bleeding several large animals immediately before the experiment. We append the protocols of two such experiments; as all the others agreed with them in every essential, it is not worth while to print them in detail.

The outcome of our work is this: that once the "aspiration of the thorax" has been eliminated, the right auricle of the mammalian heart will not receive blood unless supplied to it under a decided, if small, positive pressure. While the heart in the closed thoracic cavity may, and probably does, act as a suction pump, this is not due directly to an active expanding force of the heart, but is the secondary result of the pneumatic conditions prevailing within the normal closed chest cavity. Any cause diminishing thoracic aspiration must therefore greatly hinder the work

of the heart; and it is probably more in this manner that the circulation is impeded in certain cases by hydro- or pneumothorax than by direct pressure exerted on the heart itself.

In the experiment protocols appended there are six columns. Column I gives the time; column II, the height of the upper side of the vena cava superior from the floor on which the warm chamber rested; column III, the lowest height of the blood in the manometer tube *abm*, Plate V [Plate 5 of this volume], Fig. 1, at which the right auricle would receive blood, this height being measured from the floor of the warm chamber; column IV, the differences between the heights recorded in columns II and III, that is, the lowest pressure under which the heart would receive blood from the systemic veins; column V gives arterial pressure as measured by the manometer connected with the right common carotid; in column VI are given notes when necessary.

EXPERIMENT OF DECEMBER 2, 1886.

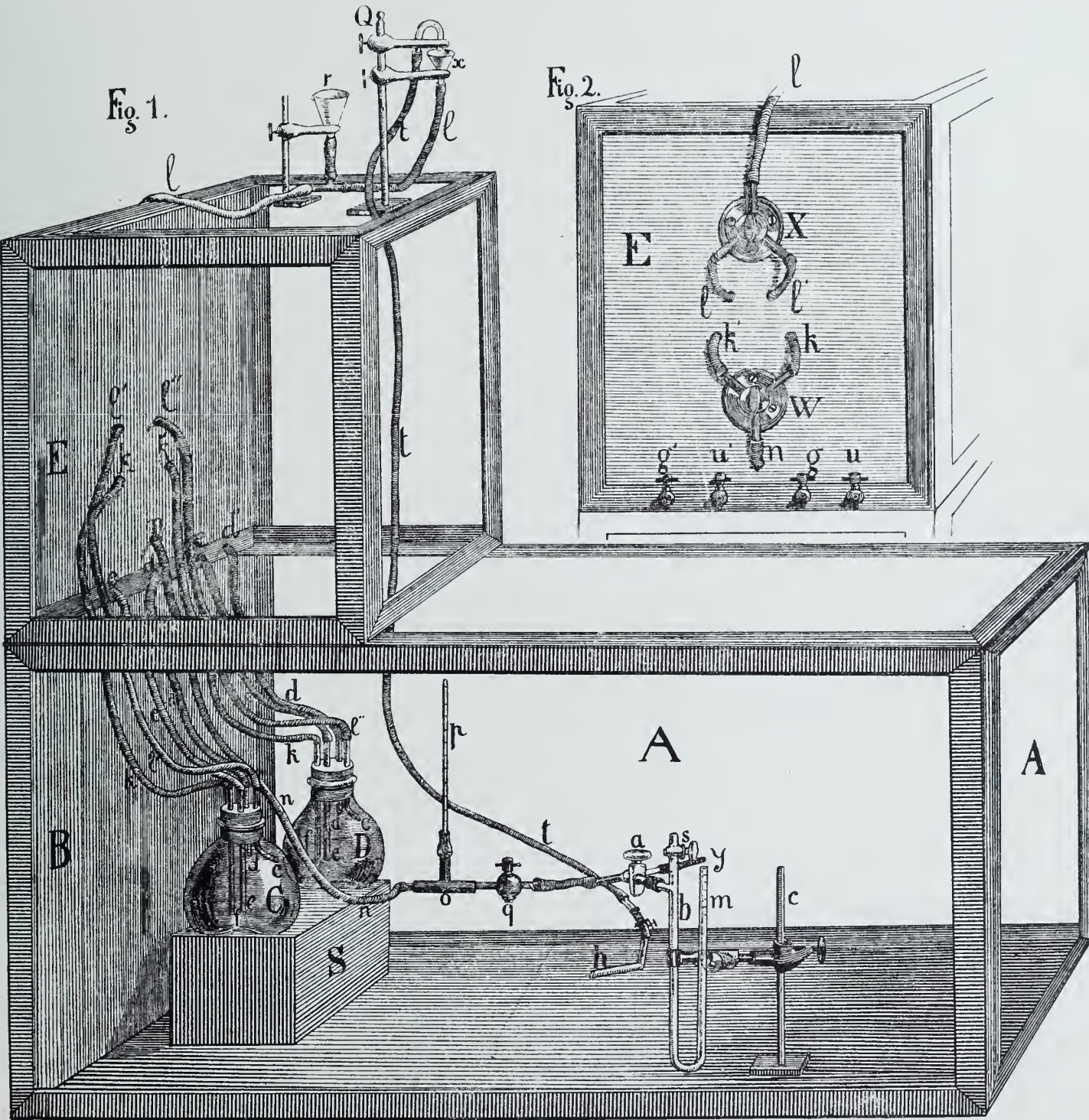
Dog under morphia and then curare.—Defibrinated dog's blood used.

I.		II.	III.	IV.	V.	VI.
Time. P. M.		Height of upper side of vena cava superior from floor of warm chamber, in millimetres.	Lowest height at which right auricle would take blood, in millimetres.	Minimum positive pressure necessary in order to make right auricle take blood, in millimetres of positive blood pressure in the vein.	Arterial pressure in right carotid, in millimetres of mercury.	NOTES.
h.	m.					
3	35	412	435	23	130	Respiration moderate and uniform.
3	38	"	447	35	164	
3	42	"	430	18	103	
3	44	"	427	15	80	
3	45	"	432	20	105	
3	46	"	435	23	142	
3	48	"	450	38	183	The apparatus for artificial respiration was readjusted at 3 h. 54' so as to make the respiratory movements of the lungs violent, both in expiration and inspiration. Artificial respiration stopped at 3 h. 55' 50". Arterial pressure again was varied, while respiration was kept constant and uniform.
3	53	"	432	20	130	
3	55	"	462	50	130	
3	56	"	432	20	130	
3	59	"	432	20	130	
4	01	"	445	33	172	
4	03	"	455	43	200	
4	05	"	442	30	135	
4	06	"	440	28	118	
4	07	"	430	18	75	
4	08	"	442	30	125	This arterial pressure was too much for the heart to overcome. It began to dilate, and the experiment was ended.
4	11	"	452	40	183	
4	13	"	512	100	205	

EXPERIMENT OF DECEMBER 3, 1886.

Dog under morphia and then curare.—Defibrinated dog's blood used.
—Respiration varied both in force and frequency during the experiment,
and at other times kept constant while arterial pressure was varied.

I.		II.	III.	IV.	V.	VI.
Time. P. M.		Height above floor of warm chamber of upper side of vena cava superior, in mil- limetres.	Lowest height at which right auricle would take blood, in millimetres.	Minimum positive pressure necessary in order to make right heart take blood, in millimetres of positive blood pressure in the vein.	Arterial pressure in right carotid, in millimetres of mercury.	NOTES.
h.	m.					
3	44	410	437	27	125	Artificial respiration 24 per minute and moderate.
3	46	"	437	27	125	Respiration stopped.
3	48	"	430	20	125	Respiration violent.
3	50	"	435	25	115	Respiration moderate, and 24 per minute from this time on.
3	52	"	435	25	85	
3	54	"	432	22	110	
3	56	"	440	30	130	
3	58	"	455	45	150	
4	02	"	480	70	170	Heart begins to dilate.
4	05	"	507	97	182	
4	08	"	455	45	125	
4	10	"	440	30	97	
4	12	"	440	30	75	
4	14	"	442	32	130	Pericardium cut away.
4	15					
4	16	"	432	22	130	
4	18	"	435	25	145	
4	20	"	437	27	165	
4	22	"	445	35	200	
4	24	"	440	30	160	
4	26	"	435	25	135	
4	28	"	432	22	100	
4	30	"	432	22	90	
4	32	"	438	28	135	
4	34	"	445	35	175	Experiment ended; heart and lungs being still in very good working condition.





VII.

ON THE TEMPERATURE LIMITS OF THE VITALITY OF THE MAMMALIAN HEART.

BY H. NEWELL MARTIN AND E. C. APPLGARTH.

With Plates 6, 7, 8.

[*Studies from the Biological Laboratory of the Johns Hopkins University,*
Vol. IV., p. 275, 1890.]

Some years ago one of us* published the results of a research showing that between the limits 27° C. and 41° C., the heart of the dog, when isolated from all other organs but the lungs, beats quicker the higher its temperature, so that by heating or cooling the blood supplied to the isolated organ through the superior vena cava, the pulse rate could be controlled.

These earlier experiments made it clear for the range of temperatures above stated, that the tendency to beat quicker at a higher temperature was a fundamental property of the heart, and that the cardiac muscle of the dog agreed in the dependence of its rhythm upon temperature changes with the histologically very different muscle tissue of the frog's heart. A question which then presented itself was, What are the limits of temperature within which the heart of a mammal will beat at all? It also seemed of interest to ascertain whether mammalian cardiac muscle agreed with amphibian in having an optimum temperature at which its rate of beat was quickest beyond which any increase would slow the rhythm, without necessarily killing the heart. That there was some such optimum for the dog's heart was rendered probable by the fact that in some of the earlier experiments† it appeared that heating the organ above 42° C. slowed its beat.

Attempts made three or four years ago to solve these problems were futile, because near the liminal temperatures, high or low, the heart beat with so little force that its death seemed rather due to deficient circulation through the coronary capillaries than to direct influence of heat or

*H. N. M. Phil. Trans. Roy. Soc. 1883, Pt. II, p. 663.

†Phil. Trans. 1883, Pt. II, table on p. 681.

cold on the cardiac muscular or nervous tissues. Our problem was, therefore, to keep the cardiac vessels well supplied with blood whether the heart beat feebly or strongly, and at the same time to vary its temperature at will. The first requirement it seemed we might attain by connecting the aortic stump of the isolated heart with a Mariotte flask filled with blood and kept at a constant level above the organ. Under such circumstances a constant pressure would be maintained in the coronary arteries, quite independent of the force of the heart's beat. If this could be done and the heart kept alive it would be easy to add arrangements for varying the temperature. A preliminary experiment or two having showed that the plan was feasible, we arranged our apparatus essentially as indicated diagrammatically in Plate XXIII (Plate 6 of this volume).

The heart was isolated in the manner described in previous numbers of this Journal, and throughout the experiment was contained in a large moist chamber, *A*; part of the roof and of one end of this are indicated at *a* and *a'* in the figure. This chamber has no floor; it sits in a shallow iron trough containing water, which, during an experiment, is heated by Bunsen's burners placed under the trough so as to keep it and the chamber warm, and the air within the chamber saturated with moisture. This air is (so far as necessary occasional opening the doors of the chamber will permit) kept at a temperature ranging between 38° and 40° C. The chamber used was that described in the first number of the fourth volume of these Studies (p. 41), and figured in Plate V [Plate 5 of this volume], accompanying that number. Most accessories had, however, to be changed when the experiments described in this article were undertaken; the Mariotte flasks, for instance, were placed outside the chamber instead of inside it; and a new form of aortic cannula had to be devised.

The animal (cats were used in all cases) was rendered insensible by inhalation of ether or by subcutaneous injection of paraldehyde, and then given curare in some cases, in others not. Paraldehyde in doses of about 5 cc. we found on the whole the most satisfactory. Tracheotomy was next performed (as a preliminary to opening the thorax), and the wind-pipe connected with the apparatus for artificial respiration. The thorax having been opened, and most vessels of the systemic circulation tied essentially as described previously,* the glass cannula shown in Plate XXIII [Plate 6 of this volume] was tied into the distal end of the aortic arch. This cannula† has three side-pieces;

*Stud. from Biol. Lab. Vol. IV, p. 36.

† The cannula was modified in the later experiments, as it was found more easy to manipulate when made in two pieces (p. 102).

through the one farthest from the heart it is supplied with defibrinated blood from the Mariotte flasks through the rubber tube *p*; through the next the most of this blood is carried off through the tube *q* and poured into a funnel; the height of this funnel above the heart of course determines the pressure in the aortic stump. A thermometer was tied into the third branch of the cannula, as shown in the diagram. All branches of the aortic arch except the coronaries were of course closed. The blood supplied to the aortic stump could thus escape only through *q* into the funnel shown in the plate, or through the circuit *q'*, indicated by dotted lines, and consisting of the coronary vessels. The blood taking the coronary circuit, on reaching the right auricle proceeded to the corresponding ventricle, and from it through the lungs to the left auricle. This blood (that taking circuit *q'*) was therefore the only blood entering the cavities of the heart or passing through the lungs, unless there were some inefficiency of the aortic semilunar valves. That the cavities of the heart were not distended with more blood, we found not to influence the normal character of its beat, which continued in many cases forcibly and rhythmically for three or four hours. The beat of the frog's heart, as well known, is much promoted by moderately high intracardiac pressure; that this is not, at least to so great an extent, the case in mammals seems easily explicable. The frog's heart, having no capillaries, depends for its nourishment or the washing out of its wastes, on the forcing of liquid under pressure into the spongy network of the ventricle, while in the mammal the nourishment of the heart depends on pressure in the aortic arch, from which the coronary system is supplied.

The side tube *q* is designed to get rid of the difficulty of insufficient aëration of the blood; were it not present, the only flow from the aorta would be through the coronary system, and the flow would be so slow that it would be impossible to renew the blood in the cannula fast enough to keep it from using up its own oxygen and becoming very venous, and unfitted to keep the heart at work. But by a free outflow through *q*, the blood in the cannula is quickly changed, and, moreover, so rapid a bubbling of air through the supplying Mariotte flask secured, that the flask takes the place of a lung and supplies arterial blood. The blood flowing from *q* into the funnel is collected in a beaker and poured every minute or two into the receiving Mariotte bottle, until the supplying bottle is nearly empty and the other full, then the stopcocks are reversed and the receiving becomes the supplying bottle, and *vice versa*.

The preceding sketch of the general plan of an experiment will probably be sufficient for most readers. In practice many unforeseen difficulties had to be overcome, which may be of interest to those desiring to further investigate the subject. A primary difficulty, which it took us long to meet successfully, was, that in a progressive heating or cooling experiment, the blood during its circuit changed its temperature so much that we could not, on interchanging the supplying and feeding Mariotte bottles, get a continuous series of observations. This was overcome by an arrangement which poured water of desired temperature into the trough containing the Mariotte bottles; thence it flowed through wide tubes forming water-jackets for the tubes *p* and *q*, Plate XXIII [Plate 6 of this volume], and then into a water-jacket surrounding the funnel receiving from *q*, and emptying into the tank containing the beakers, from which the circulating blood was returned to one of the Mariotte bottles. Another difficulty which we soon discovered was that the temperature of the heart was by no means always that of the blood supplied to it; so a thermometer inserted through the *precava*, and with its bulb reaching into the right ventricle, was used to indicate the actual temperature of the heart, instead of the thermometer in the cannula. In the tables which follow it is the record of the thermometer placed inside the right heart which is given.

The moist chamber (*A*, Plate XXIV) [Plate 7 of this volume] had on its top the two Mariotte flasks securely fastened in a tin box *B*, serving as a water-jacket. One side of *B* is of glass and turned towards the assistant to enable him to see readily when a flask is nearly empty, so that by reversing the stopcocks he may convert it from the supplying into the receiving flask. The flasks each hold about 700 cub. cent. From near the bottom of each passes the outflow tube, which is conveyed through the spouts *h* of the tin box into the warm chamber, and is continued by the rubber tube *T* (the left one is for the greater part omitted in the plate), to an aperture in the end of the warm chamber through which it passes to one leg of the Y-piece *q*, Plate XXV [Plate 8 of this volume]. Each upper leg, *j*, of the Y-piece has a stopcock on it (*bs*), so that the supply may be taken from either Mariotte flask at pleasure.

Each Mariotte flask is closed air-tight by a rubber cork pierced by three glass tubes (Plate XXIV) [Plate 7 of this volume]; one of these, *o*, is connected by a Y-piece with the funnel *P*, from which it gets blood when acting as receiving flask; a second, *n*, serves to let air out as blood enters the flask; both *n* and *o* are of course closed when the flask is acting as supply bottle to the heart. The third tube, *m*, reaches to near the bottom of the flask, and through it air bubbles in when the flask is acting as supply bottle. From its upper end passes the rubber tube, seen again at *m* in Fig. 1, Plate XXV [Plate 8 of this volume], where only the tube of one side is drawn; of course in actual use there must be a like tube attached to the other Mariotte flask. The long rubber tube *m* passes through the cork of a tightly closed test-tube, *Tb*, containing a little water. Another tube, *at*, passes to near the bottom of the test-tube and is open. When the Mariotte flask is at work all the air entering it must first bubble through the water in the test-tube, which, hanging outside the chest and the water-jacket, is easily observed, and indicates how fast the blood from the flask is flowing, or if the bubbling stop, that something has gone wrong and the supply bottle has ceased to act as a Mariotte flask. It is not necessary to describe in detail the stopcocks which lie

on all the tubes so that they can be in a moment closed or opened when the functions of the two flasks are to be reversed.

All the system of blood-carrying tubes is inclosed in a set of water tubes continuous with the spouts *hh* of *B*, and having warm or cold water from *B* flowing steadily through them during an experiment. Over those ends of each of the spouts which open into the warm chamber is fitted thin rubber tubing $1\frac{1}{2}$ inches in diameter; these tubes surround the blood-conveying tubes *TT*, and finally end (Fig. 2, Plate XXV) [Plate 8 of this volume] in *J* and *J*, which open into a funnel-shaped tin water-jacket. Inside this jacket the Y-piece *q* (Fig. 1, Plate XXV) [Plate 8 of this volume] is placed, and its upper limbs *jj* pass through *JJ* to join *TT*. On the sides of the tin jacket are openings through which pass the handles (*bdr*, Fig. 2) of the stopcocks *bs bs* (Fig. 1).

The lower limb *Q*, Fig. 2, Plate XXV [Plate 8 of this volume] of the tin jacket surrounds *q*, Fig. 1 (which conveys the blood again into the warm chamber) and is continued over *C*. This tube (*C*, Plate XXIV) [Plate 7 of this volume] leads to the aortic cannula *a*, and up to about six inches from that point is jacketed by a wide rubber tube. At this point the jacketing tube is securely closed by a rubber stopper, through which a glass cannula, *a*, continues the blood-carrying system to the aortic stump. The reason for stopping the jacketing for a short distance at this point is to facilitate insertion of the cannula.

So far, then, it will be seen that water supplied to *B*, Plate XXIV [Plate 7 of this volume] will flow out through the wide tubing surrounding *TT* through the jacket *JJ* (Plate XXV) [Plate 8 of this volume] to the tube around *C*, keeping the blood under essentially the same temperature conditions during its whole journey from the supply bottle to the heart. From near the rubber cork closing the jacket of *C* the water finds its exit through a side branch, a wide rubber tube surrounding *e*, and so to the wide glass funnel *f*, Plate XXIV [Plate 7 of this volume]. This funnel has a short stem into which is accurately fitted the stem of the blood-receiving funnel (*R*) by means of rubber tubing. From *f* the water issues through the outflow piece through the jacketing hose *l* into the tin kettle *y* (Plate XXV) [Plate 8 of this volume], containing the beakers for catching the blood; and finally into the waste bucket through the tube *Wst*.

The only parts of the blood-conveying system, then, which are not jacketed are the funnel *P*, the tubes *oo* leading from it to the Mariotte bottles, and the cannulas near the heart with a few inches of adjacent tubing. With the exception of the funnel *P*, however, most of these, including the innominate and aortic cannulas, were packed in a layer of cotton wool, thus checking any rapid loss or gain of heat.

All the water-jackets, or rather the whole jacket, for the system is but one, are supplied directly from the water pipe of the room. This pipe by means of a T-piece is connected with an air chamber whose capacity is 18 gals., and which is capable of standing a high pressure to the square inch. From the bottom of this chamber a delivery pipe, *W*, Fig. 1, Plate XXV [Plate 8 of this volume] runs to terminate in the stopcock *D*, which stands in connection with a two-way stopcock *C*, by means of which the current of water can be shunted either to the heater, *H*, or in the case of a cooling experiment to a worm (not represented in the figure) placed in a freezing mixture and substituted for the heater. In this way a constant stream of any desired temperature may be obtained.

The heater consists of about 30 feet of small brass pipe wound into a coil and placed over a small Bunsen gas-stove. The stove and coil are entirely surrounded by the screen (*Scr*) provided with its chimney, *H*. Before the water passes to the heater, however, it is made to go through *Ww* to a worm of 25 ft. of $\frac{1}{2}$ -inch bore lead pipe put in the hot water of the pan which forms the floor of the moist chamber. After traversing this worm it comes to the heater through *Hw*. In this manner the stream of water can be warmed even before it reaches the heater. The temperature of the water may be regulated by withdrawing the worm totally or in part from the water in the floor of the chamber, by the amount of gas burned, and by the rate of flow of the water. Of course in a cooling experiment this second worm was not used.

After issuing from the heater (or, in the case of cooling experiments, the worm in the freezing mixture) the stream is directed by *Rw* through the registering apparatus (*Rg*) where its temperature is ascertained. This apparatus is simply a T-piece, one leg of which carries a thermometer. From this the water passes up *Bw* (Plate XXV) [Plate 8 of this volume] to the jacket *B* (Plate XXIV) [Plate 7 of this volume] and is then distributed over the whole system just described.

Dr (Fig. 1, Plate XXV) [Plate 8 of this volume] is a small sliding door which gives the assistant access to the interior of the case during the experiment. While an experiment is going on, the main doors of the moist chamber are opened as little as possible.

As will be seen, the cannula in Plate XXIV [Plate 7 of this volume] differs in detail from that shown in the diagram, Plate XXIII [Plate 6 of this volume]. It is made in two pieces. One, *a*, is inserted in the aortic stump, and receives blood from the Mariotte flask. By its side branch *k* it was in some cases connected with the manometer of a kymograph. The other piece, *i*, is inserted in the innominate artery and contains a thermometer bulb. From it the tube *e* carries off the excess blood to the funnel *R*.

An attempt was made at first to get a graphic record of the pulse, by connecting a manometer with the aortic cannula; but the quantity of blood reaching the left ventricle was so small that the pulse waves due to its beat were indistinct and sometimes imperceptible. We had therefore to resort to counting by direct observation of the heart, which may have led to slight errors when the pulse was very fast and very feeble, but as our object was not to study the absolute pulse rate, small errors in regard to it were of no great importance. Moreover, by always taking two counts immediately following one another the chances of error were greatly lessened. First, one of us held the watch for thirty seconds while the other counted the heart beats. Then the duties were reversed and the other made the count, still being ignorant of the number arrived at by the previous counter. If the two counts did not agree, but differed only by three or four in a minute, their average was put down in the tables as the correct rate; if the difference was greater (as was sometimes the case when rapid changes of temperature were occurring) a fresh count was made or the observation rejected altogether.

In all cases at least half an hour was allowed to elapse after complete isolation of the heart before the actual experiment commenced. This

was in order to eliminate possible disturbing elements, as irritation of the vagi or accelerators, due to the operative procedure, or the first effects on the heart itself of the defibrinated blood. The general results of the experiments can be stated in few words.

First, as to cooling. The isolated heart of the cat may be cooled down to a temperature of 16.5° C. (as indicated by a thermometer introduced into the right heart) and yet not be killed, as it revives if soon warmed again (see Table I), but it usually dies at about 17° or 18° C.

As the cooling proceeds, the pulse becomes slower and slower; this has two causes. As pointed out in previous papers, after about the first half-hour the pulse rate of the isolated heart tends to become slower the longer its isolation; so that a dog's heart isolated for one hour and beating, say, 220 times a minute at a temperature of 39° C., will at the end of two hours and at the same temperature beat only 200, or perhaps 190 times a minute. But the slowing in such cases is very gradual, and the heart will beat vigorously for four or five hours if not cooled. When the influence of cold is added, the fall in the pulse rate is far more rapid, and death of the isolated organ, if the cold be continued, occurs much sooner than it otherwise would.

TABLE I.

Cooling experiment with recovery, June 13, 1888.

Adult cat narcotized with paraldehyde during isolation of the heart. Isolation completed at 3.30 P. M.

Time—P. M.		Temperature C. in Right Heart.	Pulse per 1'.	Remarks.
h.	m.			
4	08	34.0	183	
4	11	33.7	175	
4	14	32.7	158	
4	17	30.9	138	
4	20	29.9	124	
4	23	28.5	111	
4	26	28.5	92	
4	29	26.7	80	
4	32	25.7	74	
4	35	24.7	66	
4	38	24.0	61	
4	41	23.5	54	
4	44	23.0	53	
4	47	22.3	50	
4	50	21.7	40	
4	52	20.5	?	
4	56	19.9	?	
5	00	19.5	12	
5	04	19.2	11	

TABLE I.—*Continued.*

Time.		Temperature C. in Right Heart.	Pulse per 1'.	Remarks.
h.	m.			
5	06	18.9	9	
5	12	18.6	9	
5	15	18.0	9	
5	20	16.5	5	Heating now commenced.
5	40	21.0	14	
5	45	24.0	20	
5	50	27.3	78	Contractions becoming very feeble.
5	56	29.7	85	
6	06	31.7	90	

The results obtained on heating the heart to or near to its death point are more complex than those observed on cooling, but also more interesting.

In the first place we found that there was an *optimum* temperature at which the isolated cat's heart, like that of the frog, beat quickest, any rise beyond this slowing the beat. It by no means follows, of course, that this optimum is the temperature at which it would do most work. Averaging the results of thirteen separate experiments, this optimum is 41.3° C., ranging between 43.3 and 40.6.

If one steadily and slowly heats the heart to the highest temperature to which it can be raised without dying, this lethal temperature lies between 44.5° and 45° C. in the great majority of cases; but sometimes by working with care, one can raise this *maximum* as well as the *optimum* temperature. If as soon as the heat is beginning to slow the pulse, or the heart shows other signs of weakening, the organ be cooled for a short time and then heated again, it can often be raised to a higher temperature without being weakened, and the *optimum* temperature also raised. Table II will serve as an example of a simple maximum and optimum experiment, while in Table III is given an example in which the optimum is raised by slightly cooling the heart from near the lethal temperature and then very slowly heating it again. This power of the heart to rapidly accommodate itself to an abnormally high temperature was so surprising to us that we made repeated observations on the matter. Since then we have been informed by friends engaged in the practice of medicine that something similar is frequently seen in persons suffering from remittent fevers. A rise of temperature associated with considerable quickening of the pulse may, later in the disease, be associated with a less marked quickening.

When the temperature of the heart rises to about 40° C., even though the optimum be not yet reached, small increments of temperature often have no effect on the rate of beat of the isolated heart, or the pulse may even become slower: this no doubt is due to that natural gradual slowing of the pulse of the isolated heart, always occurring as time goes on, and referred to above.

Another phenomenon often observed in heating experiments is what we may call a long latent period. An increase of temperature may not show any effect on the pulse rate for a minute or two, then it comes on, though the heart may in the meantime have been slightly cooled. For this reason (even before the optimum is reached) variations in the pulse curve tend to lag a little behind the temperature variations which led to them.

TABLE II.

Simple heating experiment to show optimum and maximum. June 7, 1888. Adult cat. Paraldehyde. Isolation of heart completed at 11.15 A. M.

Time.		Temperature C. in Right Heart.	Pulse per 1'.	Remarks.
h.	m.			
11	51	34.1	168	
11	54	34.8	174	
11	57	35.2	186	
12	00	36.5	188	
12	03	36.9	186	
12	06	38.3	189	
12	09	38.8	190	
12	12	40.0	200	
12	15	40.3	201	
12	18	40.5	200	
12	21	40.5	200	
12	24	41.2	203	
12	27	41.2	202	
12	30	41.0	200	
12	33	41.8	206	
12	36	42.5	209	
12	39	43.2	210	Optimum or probably rather above it.
12	42	44.7	160	
12	44	45.7	?	Pauses alternating with periods of very rapid beats impossible to count.
12	47	46.0		Fibrillar contractions.

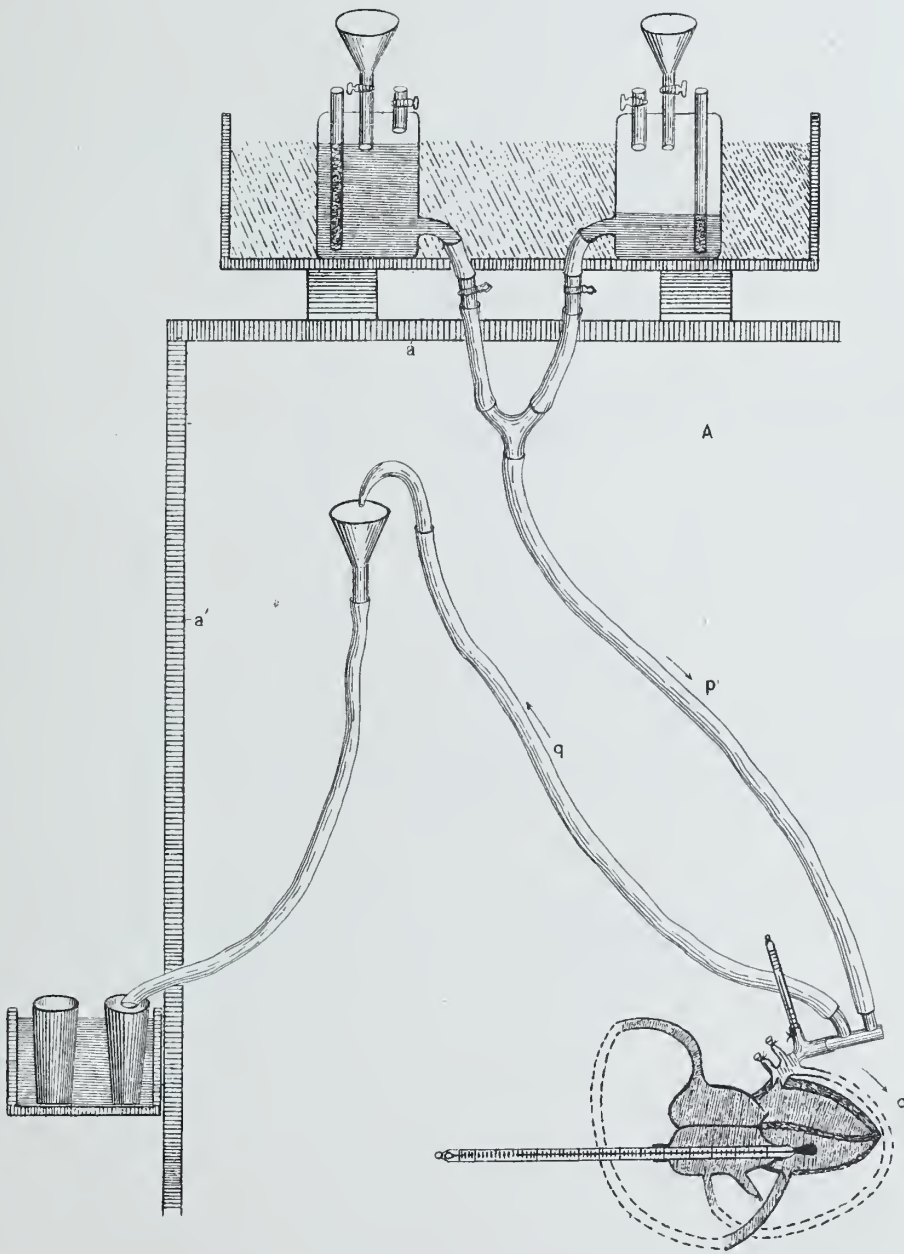
TABLE III.

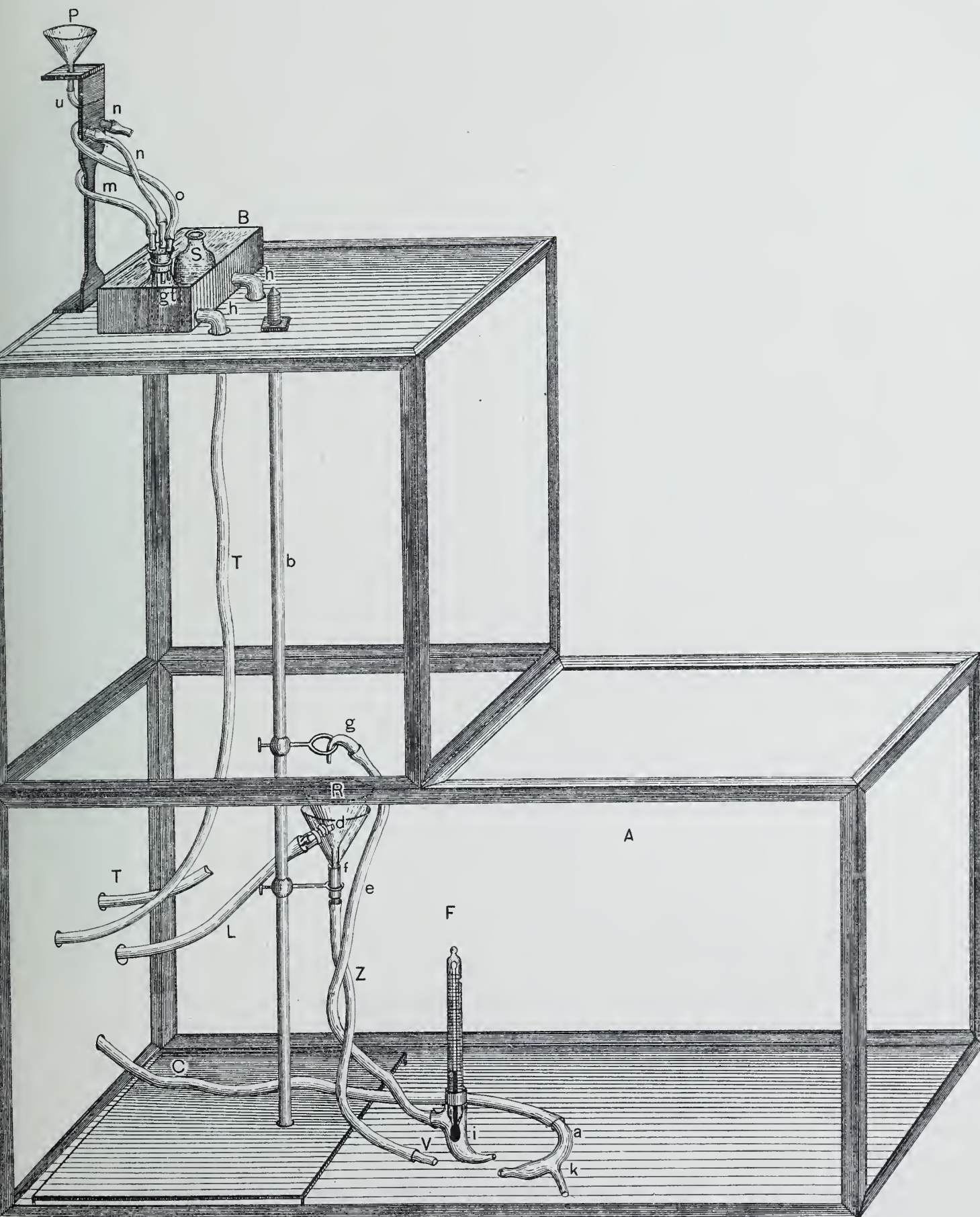
Optimum temperature raised during an experiment. January 31, 1889. Young cat. Ether and curare. Defibrinated blood used to feed the heart, diluted with one-third its volume of normal saline. Isolation completed at 2.55 P. M.

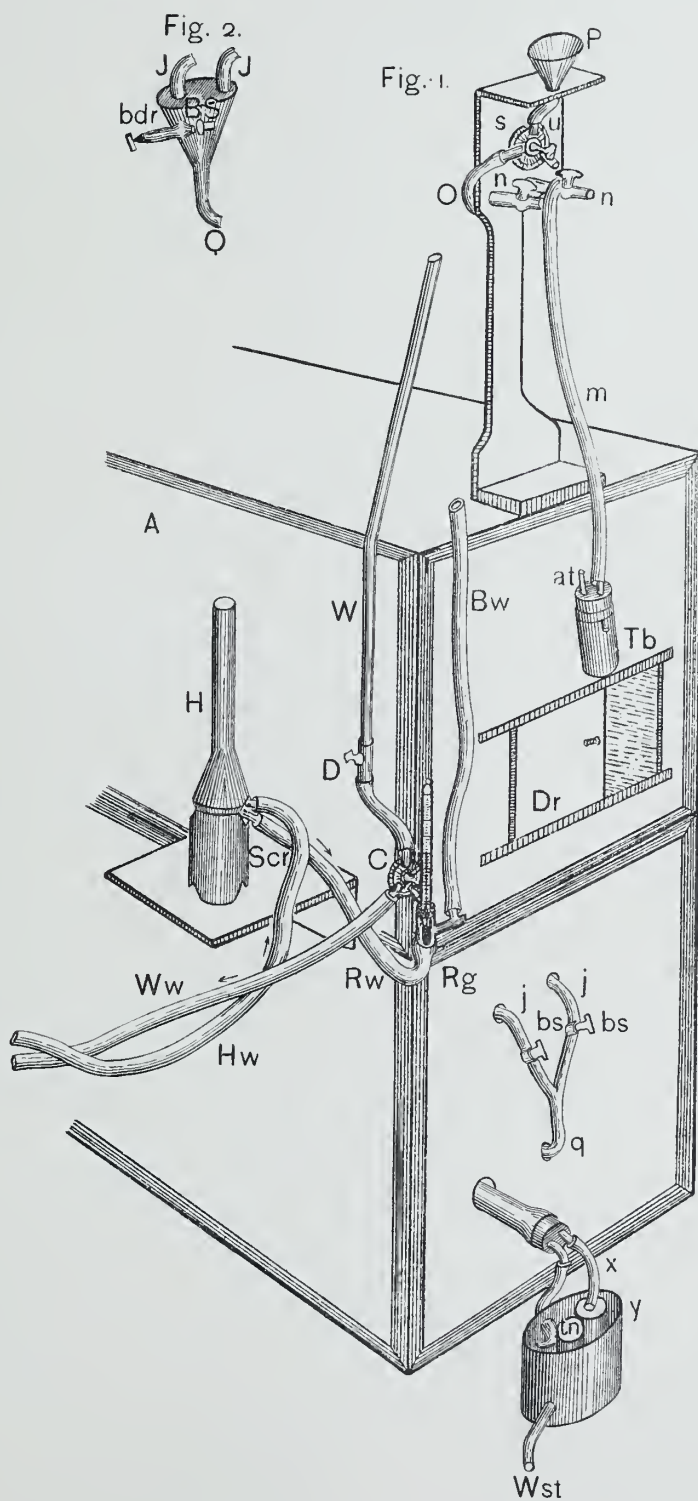
Time.		Temperature C. inside Right Heart.	Pulse per l'.	Remarks.
h.	m.			
3	51	39.3	234	
3	55	39.5	236	
3	58	39.5	220	
4	01	39.8	245	
4	03	40.3	240	
4	06	41.0	292	Temperature now raised with great care, as heart is near its critical point.
4	09	41.0	280	
4	12	41.0	272	
4	15	41.5	304	First optimum.
4	18	41.5	?	Irregular and not countable.
4	22	41.5	246	Regular. Heart apparently getting used to this temperature.
4	25	41.0	248	
4	28	41.0	204	
4	31	40.5	208	
4	34	41.0	204	
4	37	41.8	224	
4	40	42.0	?	
4	43	42.0	228	
4	46	42.5	234	Second optimum 1° C. above the first.
4	48	42.8	188	
4	51	42.3	198	
4	54	43.0	200 (?)	Somewhat irregular.
4	57	43.5	178	Regular.
5	00	43.0	178	
5	04	42.5	176	
5	07	42.8	176	
5	10	43.0	168	
5	13	44.5		Very irregular.
5	16	44.0	176	Regular.
5	19	48.0	172	Very irregular but not feeble beats; the irregularity probably due to the rapid change of temperature.
5	21			Only right auricle beating.

It is, of course, not possible to say at what temperature the heart of Table III would have died had the heat been slowly pushed on at 4 h. 18 m., instead of stopping and cooling from 4 h. 25 m. to 4 h. 34 m., thus giving the organ time to accommodate itself to the high temperature. But from many other observations in which the heating was slowly pushed on, we feel sure that all pulsation would have ceased at a temperature several degrees below 48° C.

It will be observed that though the temperature of the second optimum is higher than that of the first, the pulse is slower, this being no doubt due to the increasing malnutrition of the heart as time goes on.







VIII.

OBSERVATIONS ON THE MEAN PRESSURE AND THE CHARACTERS OF THE PULSE-WAVE IN THE CORONARY ARTERIES OF THE HEART.

BY H. NEWELL MARTIN AND W. T. SEDGWICK.

With Plates 9, 10, 11.

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While for a considerable number of years careful studies of the blood-flow in various arteries of the mammalian body have been made under different conditions, the arteries of the heart itself have remained in an exceptional position. The average pressure and the pulse characters in them have been unknown, in spite of the recognized fact that great interest and importance belong to their study.

The following pages give an account of experiments undertaken with the object of gaining some knowledge of these points, and contain, we believe, a description of the first successful attempt to record graphically, as in other arteries, the blood-pressure and its variations in the arteries of the heart. They were begun in the first place for the purpose of testing the theory of Thebesius—a theory independently propounded and warmly supported in recent times by Brücke, and others, concerning the physiology of the aortic semilunar valves. According to this theory, during ventricular systole the thin flaps of the valve are pressed upwards and cover the mouths of the coronary arteries, completely closing them, so that blood can enter these vessels only during the time of ventricular diastole and during that small portion of the systolic period which is occupied by the valve in traveling from its diastolic position across the mouth of the aorta, to its systolic position against the aortic wall and over the mouths of the coronaries. Observations on the spirting of blood from a cut coronary artery have shown this to be synchronous with systole of the ventricle; but to the value of these observations Brücke* has raised two objections. First, that merely opening the pericardium is

* Vorlesungen, 1881, S. 185.

enough to destroy the normal action of the heart and consequently of the valve under consideration; and, second, even supposing it does not thus interfere, that the brief period before the valve-flap closes over the coronary (and during which the coronary blood must share the rise of aortic pressure due to commencing systole) is quite sufficient to cause a systolic spirting, especially if the outflow from the heart vessels is hindered by the increasing cardiac contraction compressing the smaller branches in the heart walls. The first objection seems to us trivial when only a small slit over the artery is made in the pericardial sac; but the second is more formidable. We know that in the first stage of the systole, before the valve can close over them, a rise of pressure must take place in the coronary trunks. To urge, therefore, that mere observation of spirting from the cut end of such a trunk can settle the question, is to claim that the unaided eye can distinguish between a rise of pressure only occurring early in the systolic period and a rise caused directly by the systole of the ventricle and lasting all through it. Considering how little time is needed for a complete contraction this is clearly impossible. Again, with our previous ignorance of the events transpiring in the cardiac vessels, and with no experimental evidence of increase or diminution of resistance in the smaller twigs during the systole, it is quite conceivable that some spirting might occur during that period, owing to the simultaneous effects of hindrance to the outflow and of increased pressure exerted upon the vessels by the contracting tissue. In a case like this, which calls for accurate observation and comparison, the graphical method is the only satisfactory one; and as numerous attempts to settle the question at stake, based on other methods, have given rise to great diversity of opinion, we set to work to obtain, if possible, simultaneous records of the blood pressure and pulse waves in the coronary and carotid arteries.

Although the opposite view has from time to time been upheld by many anatomists and physiologists, nevertheless Brücke has so skilfully defended his theory that it is accepted by many physiologists to-day; we, at least, prepared for our experiments with a decided leaning toward his view, and began work in the hope of establishing it more firmly. The results of our investigation, however, have forced us to believe that the semilunar valve does not act as Brücke supposes, and that his theory is no longer tenable. Apart, however, from this point, we venture to believe that the work possesses interest of its own; and that the discovery that it is quite possible to get tracings of the blood-pressure in the arteries

of the dog's heart lays open a considerable field for investigations upon the mammalian heart in general—an organ which has hitherto been somewhat baffling to the physiologist.

Our experiments have all been made on dogs placed under the influence of a full, or rather an extreme, dose of morphia—from one to two grams of the acetate given subcutaneously in watery solution. While this drug greatly slows the respirations and somewhat later, to a certain extent, the rate of the heart's beat, it seems in no way to impair the vitality of this organ; if anything it appears rather to increase its capacity for bearing insults—a matter deserving of further investigation. The animal having been put very completely under the influence of the drug, tracheotomy was performed, a cannula placed in one carotid artery, and the pneumogastric nerve of the same side exposed and divided so that its peripheral end was ready for stimulation.

An incision was then made in the middle line along the manubrium of the sternum; the muscles, etc., were dissected from the first pair of costal cartilages, and (the apparatus for artificial respiration having been connected with the windpipe) the cartilages of the first pair of ribs and the bit of sternum between them were removed, thus laying bare the apex of the chest cavity, which was then opened. The artificial respiration was now stopped for a few seconds, so that the lungs might collapse and thus expose on each side the internal mammary artery, running along the exterior of the mediastinum and the remnant of the thymus, to the ventral aspect of the chest wall opposite the second costal cartilage. These arteries having been tied, the incision along the middle line was prolonged backwards and the skin and muscles reflected on each side so as to expose the rib cartilages. This operation is usually accompanied by only an inconsiderable venous oozing after the internal mammary arteries have been secured in the manner just mentioned.

The sternum and costal cartilages were then removed, care of course being taken not to injure the lungs. The next step was to stitch the pericardium to the chest wall in order to support the heart and prevent its receding too much when the lungs empty during expiration.

Branches of the coronary artery can now be seen through the pericardium, and a window is so cut in that membrane as to expose a branch which seems suitable, while all the rest of the heart remains protected and supported by its sac.

So far the operative procedures are tedious but present no special difficulty; but to lay bare the coronary branch and to fix the cannula

in it while the heart continues to beat is much more troublesome, since any carelessness in these operations is apt to so far injure the heart as to destroy its normal beat and throw the ventricles into incoordinate fibrillar contractions, from which we have never seen them recover. The success of the attempt depends largely on the animal; in the most favorable cases the left coronary artery, after giving off its transverse branch, which runs along the auriculo-ventricular groove, passes along the septum ventriculorum on the ventral aspect of the heart, and gives off near the base of the ventricle a considerable branch to the right, which runs with a vein on each side of it, and is covered only by the visceral layer of the pericardium and some fat. Into this branch the cannula is inserted, and the blood carried by the main trunk and its remaining branches serves perfectly to keep the heart beating vigorously for several hours, as we have repeatedly found. In other cases the artery does not give off this one main branch, but (especially in large dogs) runs along the ventricles, giving off small twigs right and left which are too minute for the convenient introduction of a cannula, and are, moreover, often covered by a thin layer of the musculature of the heart in addition to the pericardium. This muscular layer adds greatly to the difficulty of successfully isolating the artery, for any wound to the proper cardiac substance about the vessels seems more fatal to the organ than anything else. Soon after such an injury it almost invariably exhibits periodic beats for a short time and then the ventricle passes into a state of fibrillar contraction. The well-known fact that needles may be thrust into many parts of the heart without essentially influencing its beat for a long time, inclines us to the belief that the result in the cases to which we refer is perhaps due to the injury of nerve trunks which may run in the heart near its arteries and which are torn with the muscle, rather than to direct injury of the muscular substance; but we have not yet had an opportunity to examine this point.

A suitable coronary branch having been found, the next step is the most difficult in the operation, viz., to tear through the visceral pericardium over the artery without opening that vessel or its accompanying veins; for the membrane is so smooth and tightly stretched that it is not easy to catch hold of; and then so tough that it is difficult to penetrate. Our method is as follows: All being ready, the pneumogastric trunk is stimulated so as to stop the heart's beat, and the artificial respiration simultaneously suspended so as to avoid movements of the heart due to contractions and expansions of the lungs. With a sharp-pointed pair of

forceps the pericardium over the artery is seized and a hole torn through it by means of a needle; once this aperture is made through the tough membrane without injuring any of the vessels the rest of the operation is comparatively easy. The stimulation of the pneumogastric is stopped and the artificial respiration resumed for a moment or two; then the heart-beat and breathing are again suspended, the edge of the hole is taken in the forceps and the membrane over the artery slit up toward the base of the heart by a very fine-bladed knife. From time to time, as the heart begins to beat in spite of stimulation of the pneumogastric, the nerve is allowed to rest and the respiration is resumed, and in this way the alternate stimulation and rest are repeated as often as may be necessary in order to expose a sufficient length of the artery, to place ligatures around it, and insert a cannula in the manner adopted for any other artery. The carotid is then connected with one mercury manometer, the coronary branch with another, and, the pens being arranged so as to write exactly over one another, tracings are taken on the kymographion.

The mode of connection of the arteries with the manometers demands a word. In the first place, the three inches of the arterial end of the connecting tube between the coronary and its manometer consist of highly flexible rubber tubing. This, no doubt, slightly modifies the pulse-waves on the tracing, but it gives to the heart free play during each beat, since the flexible tube offers no restraint but yields readily. This soft tubing is succeeded by a glass tube, which is firmly held by a solid support, so that no locomotion of the tubing occurs beyond this point.

Movement of the bit of flexible tubing attached to the cannula does slightly alter the level of mercury in the manometer, but, as we have satisfied ourselves by careful examination, causes no features in the tracing which can be mistaken for a pulse-wave. Beyond the piece of glass tubing mentioned above, the connecting arrangement is similar for the two arteries.

To get a true base-line, or line of no pressure, for each manometer gave us some little trouble. The base-line is often taken as that drawn by the pen when the mercury stands at the same height in both legs of the manometer, but this is seldom correct. If the end of the connecting apparatus attached to the artery be above the level of the mercury in the limbs of the manometer with which it is joined, the weight of the liquid in it will affect that level, making it sink in the nearer and, of course, rise in the farther limb which bears the pen. If, on the other hand, as is more often the case, the arterial end of the connecting tube be below the

level of the mercury in the gauge the tube acts like a siphon-tube; the mercury rises somewhat in the proximal limb, and sinks to the same extent in that which carries the pen, so that in either case the base-line drawn with the two mercury columns level will be incorrect.

As we wished especially to compare the amount of arterial pressure in the coronary with that in the carotid, we had to eliminate such errors, and the more so because the manometer attached to the coronary artery was invariably above the one connected with the carotid, and so the siphon action (for the ends of the tubes farthest from the kymographion were always below the levels of the mercury in the manometers) was considerably greater. The method which we adopted gives, we think, absolutely true results. Having finished an experiment, we stopped the artificial respiration, and let the animal die of asphyxia, the manometers being meanwhile shut off from connection with the arterial system. When the animal was quite dead, and all traces of arterial pressure had disappeared, the communication with the manometers was again opened, and the pens, of course, fell with the mercury to the level which corresponded to zero arterial pressure: we, of course, satisfied ourselves that there were no clots in the apparatus. The pens were then turned away from the paper, which was next recoiled on the drum until the beginning of the record of the experiment was reached; then, the pens being turned back again, the kymographion was started once more and each pen drew its own base line, being still connected with its artery and the position of the animal being the same as during the experiment. It has been suggested to us that the base line so obtained may not be reliable as some arterial pressure might still remain in either the carotid or coronary vessel, or in both, after general death; but this objection we think will not bear examination. After death from asphyxia, as is well known, the arterial system, at least in its larger trunks, is extremely empty; a few minutes after its occurrence one may cut the aorta without the slightest spirt of blood resulting, and, indeed, even almost without bleeding at all; and the carotids, subclavians, and other large arterial trunks are obviously collapsed and empty. That under such circumstances there should be any arterial pressure possibly remaining in arteries in free and direct connection with the aorta is not conceivable.

A description of the tracings taken on the kymographion (Figs. 1-5, Plates VIII, IX, X [Plates 9, 10, 11 of this volume]) will serve best to show our results. The tracings, in fact, speak for themselves, and have been selected from a considerable number which all perfectly agree with

them as to the conclusions to which they lead; we have never obtained a single contradictory record. The pulse synchronism and the similarity of the pulse-waves in the carotid and coronary under different amounts of blood-pressure and with various rates of heart-beat is remarkable throughout. In Fig. 1, Plate VIII [Plate 9 of this volume], we have a pulse rate of 132 per minute, and complete synchronism in the two arteries; the mean pressure in the former being 62 mm. of Hg and in the latter 42. The verticals, *vv*, cut all the tracings at points corresponding to the same moment of time. In Fig. 2, Plate IX [Plate 10 of this volume], is a tracing taken with a quicker pulse, about 172 per minute. At *v'*, artificial respiration was stopped so as to get a dyspnoëic rise of arterial pressure. As the verticals show, this does not disturb in the least the synchronism or similarity of the pulse-waves in the two arteries. Mean pressure in coronary, 46 mm. of Hg, and in carotid, 56, at the beginning, rising to 100 mm. and 120 mm. respectively just before *v'''*.

Fig. 3, Plate IX [Plate 10 of this volume], gives simultaneous tracings from the two arteries during extreme dyspnoëa, with greatly slowed pulse and very high blood pressure, rising in the part of the tracing given to 120 mm. of Hg in the coronary artery and to 132 in the carotid. Ultimately the pressure rose still higher, and drove the pen attached to the coronary vessel off the top of the paper, so that a record could not be obtained. The accuracy with which each tracing reproduced the other during all the variations of pressure and pulse-rate which occurred during this observation is very remarkable, and seems to make it certain that the pressure in each artery is directly determined by the same cause, viz., aortic pressure. The contracting ventricle might conceivably increase pressure in the coronary vessels by compressing them; but variations thus produced cannot be imagined as agreeing so perfectly with the variations in carotid pressure (which, on such a theory, must be under different influences) as do those given in this figure.

Unfortunately a seconds' pen was not connected with the kymographion on this occasion, so that the pulse-rate cannot be stated accurately; but by taking an average from the rate of movement in other cases it may be set down as about 60 without any great error.

In Fig. 4, Plate X [Plate 11 of this volume], is given a tracing taken soon after the resumption of artificial respiration, which has been interrupted long enough to produce (as seen to the right of the tracing) a considerable dyspnoëic rise of arterial pressure. Well marked and similar Traube's curves are seen on each tracing, and also the synchronous pulse

in both arteries. This synchronism is maintained throughout all changes of cardiac rhythm and blood pressure.

In Fig. 5, Plate X [Plate 11 of this volume], is a tracing in which the coronary pressure is higher^{*} than the carotid (76 mm. against 64 mm. Hg). This may perhaps be due to our having taken in this case a coronary branch nearer the main stem than usual; but it may also, and more probably, be vasomotor. The heart arteries have a very active system of these nerves, as any one who experiments with them will soon observe. Not unfrequently on laying bare a coronary branch that seemed suitable for inserting the cannula we have found it apparently so small that our endeavor seemed hopeless; and then in a minute or two it would dilate again to at least double its previous diameter. If it be borne in mind that the coronary branch used was always but a small twig of the whole coronary system, it seems possible that great constriction in the rest of the branches might so oppose the blood flow as to raise the pressure almost up to that in the aortic arch, and so bring it above that in the carotid.*

In other respects the tracing illustrates the same points as those reproduced in the preceding figures. The heart was beating 148 per minute.

We find then that whether the heart beats slow or fast, and whether arterial pressure be high or low, every feature of the carotid pulse is simultaneously given in the coronary. No doubt, with a faster-traveling roll of paper the synchronism would not be perfect, as the carotid vessel is farther from the heart, but the pulse-wave travels so fast that this could not be expected to be shown on the kymograph.

There is, however, no trace of any alternation in the pulse-waves, such as would seem necessarily to follow from an occlusion of the mouths of the coronary arteries during the ventricular systole, and such as the kymograph would certainly show if it existed.

The argument which was used effectively against conclusions drawn from observations upon spirting coronary arteries, may be brought

* We have recently endeavored to discover the source of the vaso-constrictor nerves of the heart, by connecting cannulae with carotid and coronary arteries and then observing if a relative rise of coronary pressure could be brought about by stimulating extrinsic cardiac nerves. So far our experiments have been confined to the accelerators and have been entirely negative. We got the acceleration of the pulse rate, but no rise or fall in coronary pressure, which was not exactly duplicated on the tracing from the carotid manometer.

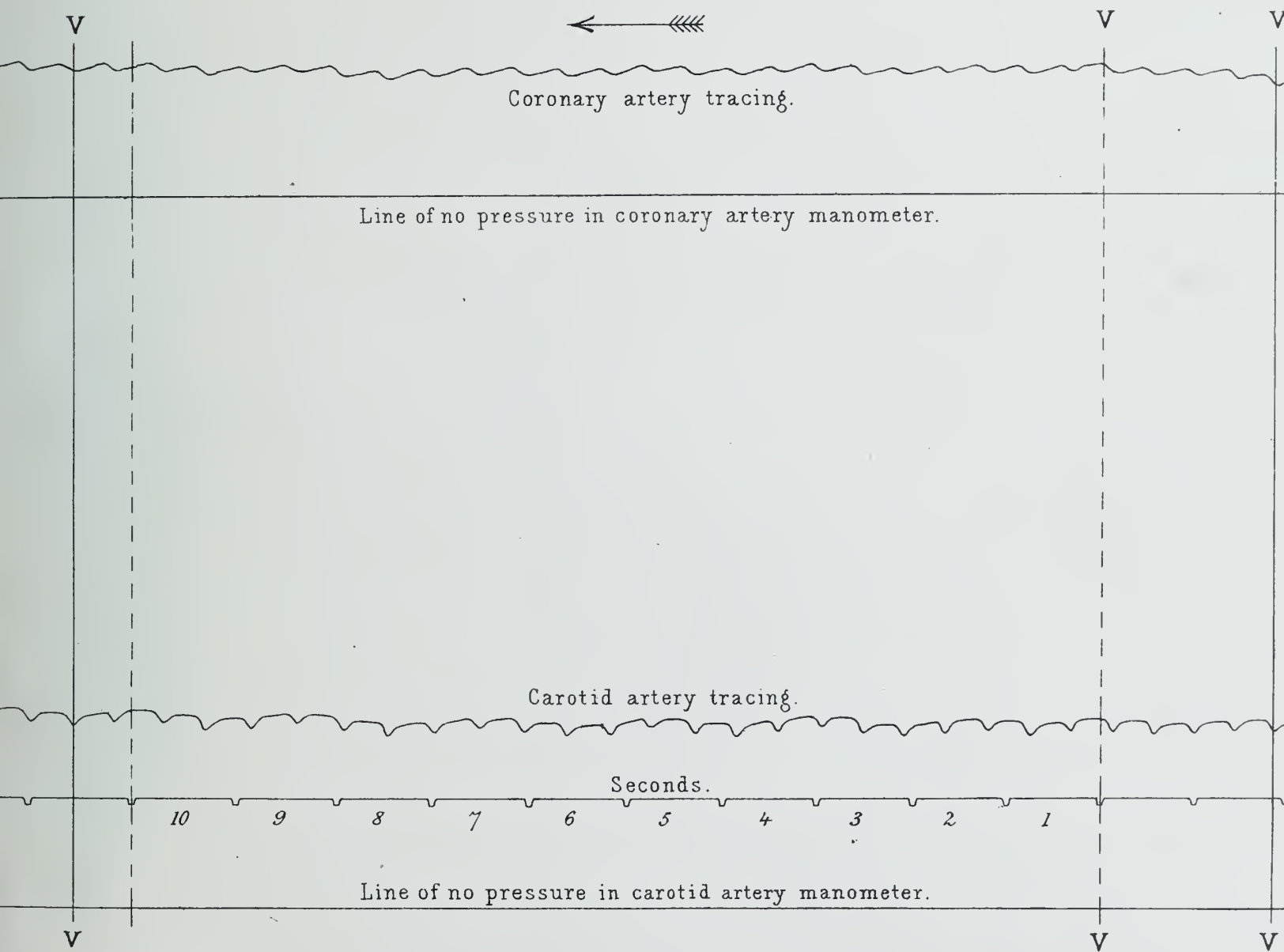
perhaps to bear upon our work, viz., that in the earliest stage of contraction of the ventricle, the coronary shares with the carotid the general rise of pressure in the arterial system, because the valve has not yet closed over its mouth; and that, in consequence, it is to be expected that the two pens which have traveled during the diastole of the previous undulation together shall together begin their systolic journey on the new pulse-wave. This is, no doubt, quite true, and we have no objection to the argument as far as it goes. It leaves off, however, where our work begins, and does not affect the real point of the question, though it emphasizes the necessity for exact tracings which can be studied leisurely.

Since the coronary artery is freely exposed to aortic pressure during all of the diastole and during the first fraction of the systole of the ventricle, we are not surprised to find, at that time, on the tracings complete agreement between carotid and coronary pulses; they are caused by the same things and are therefore similar. If now we turn to the tracings described during the major portion of the systolic period, and find them duplicates one of the other, alike in form and synchronous in character, it is hard to believe that they also are not directly dependent on the same immediate cause, *i. e.*, aortic pressure. For if the valve closes as Brücke believes, the forces acting upon the two arterial contents are no longer identical; the carotid is still marking an increasing pressure due to the outflow of blood from the energetically contracting ventricle; but the coronary, cut off by the valve from influx of blood, is put under other conditions. It is not supposable that the ventricle acting upon the carotid directly through the aorta should cause it to trace a pressure curve precisely like one drawn at the same time by the coronary, upon which it is acting only indirectly (*i. e.*, by raising intraventricular pressure, and so causing extra compression of the vessels in the heart substance). Nor is it conceivable that the coronary artery should have its mouth suddenly closed at one instant during the period of rising pulse-wave, and still go on tracing undisturbed an uniform rise of pressure. Under such circumstances some deformation of the coronary curve, some irregularity in the tracing must take place. Again, after the systole is over and the valves rebound to their position over the mouth of the aorta, a moment would come (when the period of highest carotid pressure was just past) when the coronary artery would suddenly be opened and blood would be driven into it.

An injection of blood into the previously closed coronary system at this moment ought surely (even if it did not, as may be urged, raise arterial pressure in the coronary artery, because the cardiac muscle was relaxing and making the coronary circuit easier of passage) to show itself in some break or rise, or other special feature in the pressure-changes at that moment occurring in the vessel; the tracing from the coronary vessel (now for the first time receiving blood) could not exactly agree in every respect with the tracing from the carotid artery, which is simultaneously emptying itself steadily and regularly under the force of arterial elasticity. We find, however, nowhere any indication of such events; the coronary tracing is always a duplicate of the carotid under all circumstances, and there is no sign of any periods when great circulatory changes (such as are involved in the supposition that the mouths of the coronary vessels are alternately closed and opened) are taking place in the coronary artery.

We are therefore forced to conclude that those are in the right who have maintained that the flaps of the semilunar valve are never pressed completely back against the aortic wall during systole of the ventricle. Finally we may point out that the tracings show the pressure-changes in the coronary system to be very much like those in any other branch of the aortic system—the carotid for example. It may be added in conclusion that though forced to differ from Brücke in regard to any interference of the semilunar valve with the circulation in the coronary system, our observations in no way contradict his teaching that during ventricular diastole blood flowing into the coronary arteries aids in distending the flaccid heart. This is probably true. The complete “*Selbststeuerung*” is however no longer tenable; the arteries of the heart are not emptied during the ventricular systole so as to diminish the resistance to contraction but are at that time tensely filled. Moreover, as our tracings show, the little increment of pressure during the systole of a single beat when compared with the entire mean pressure constantly at work in the coronary system is so small that after all not much would be gained by blocking the mouths of the arteries in order to avoid it.

Fig. 1.



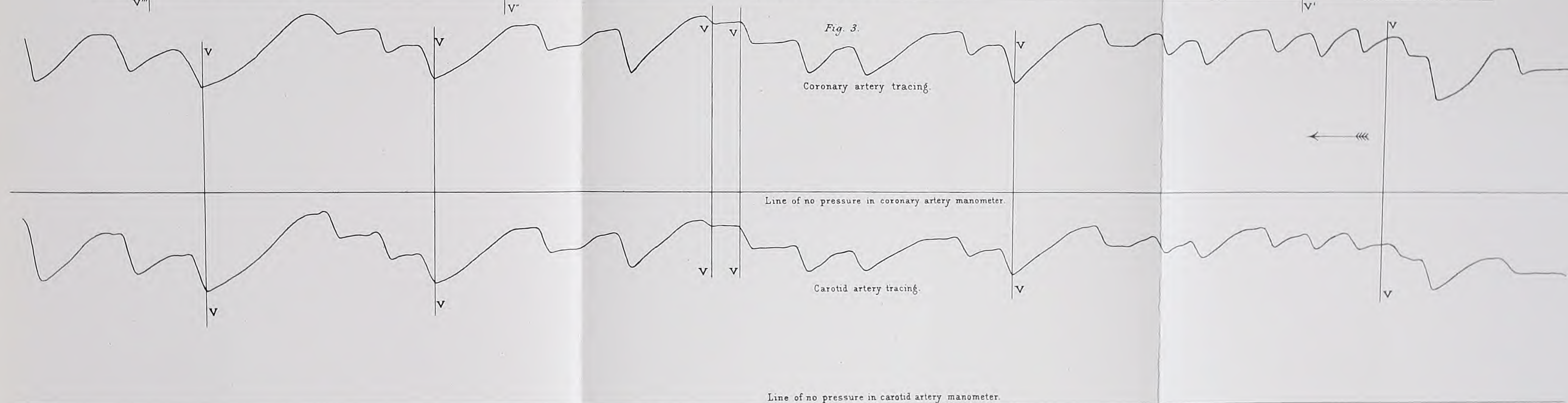
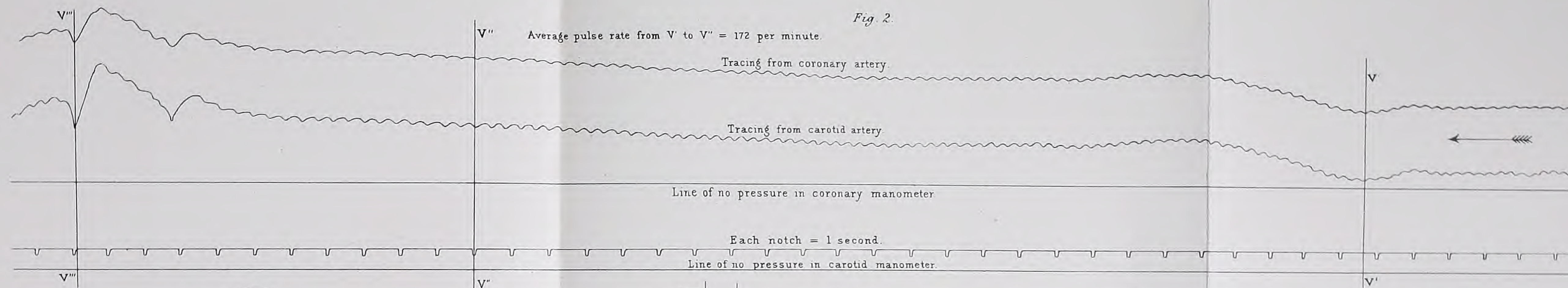


Fig. 4.

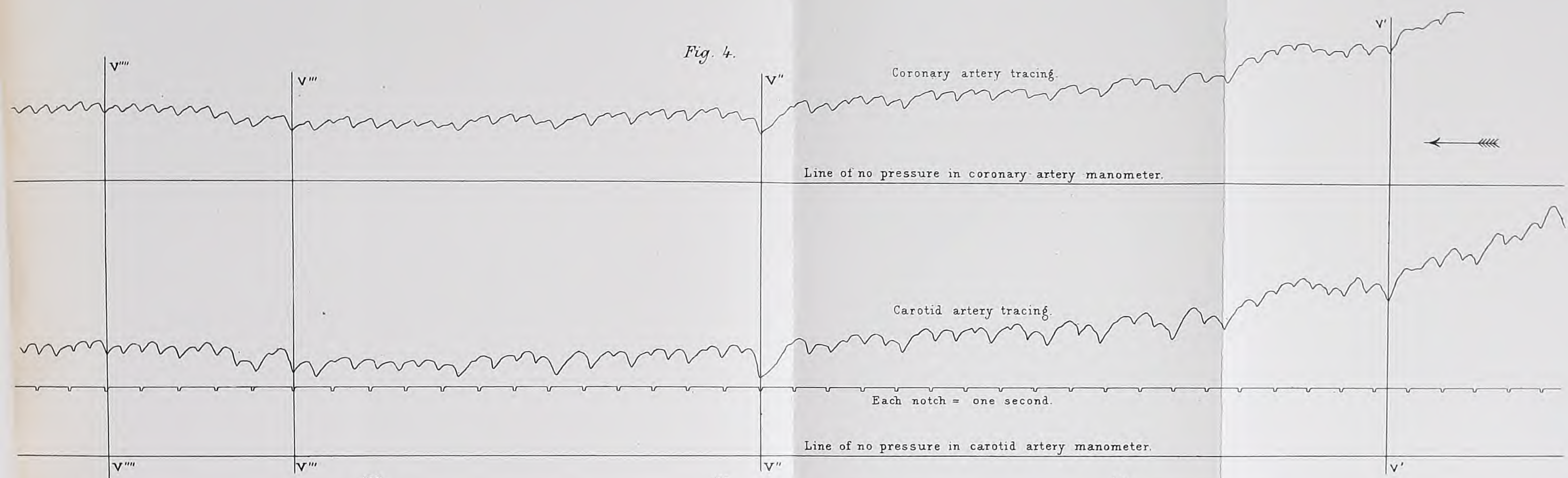
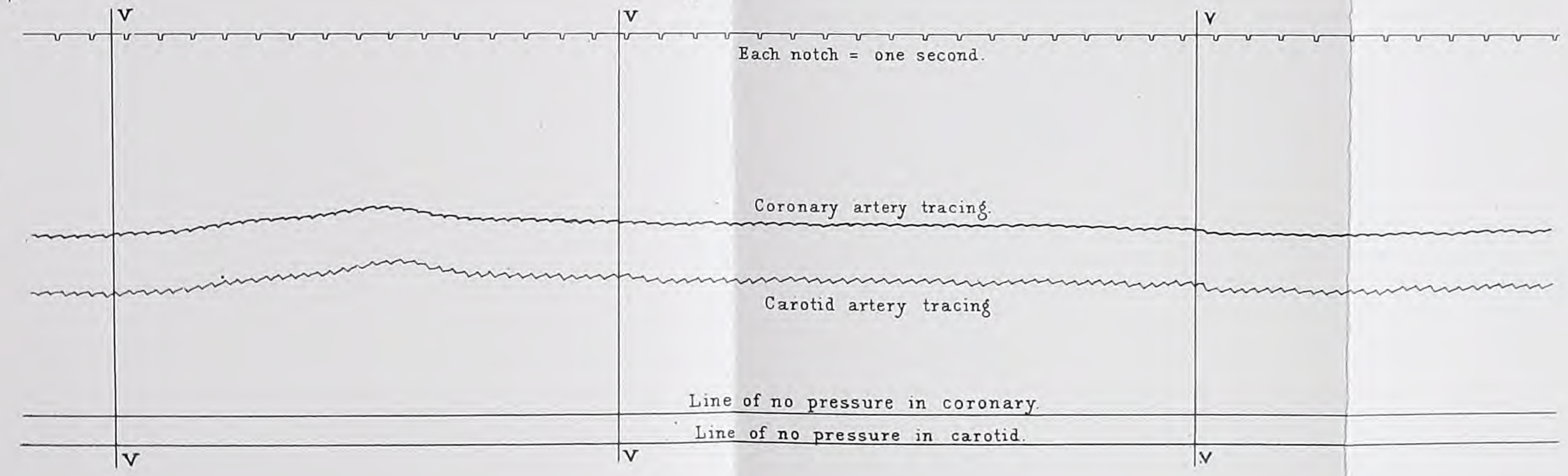


Fig. 5.



IX.

VASO-MOTOR NERVES OF THE HEART.

[*Transactions of the Medical and Chirurgical Faculty of Maryland*, 1891.]

There has come about in physiology within the last ten years the use of two new words, *anabolic* and *katabolic*. The justification for the employment of these words is mainly to be found in recent experiments made on the heart which show that certain nerves tend to help the nourishment of the heart and are in the old sense of the word, true *trophic* nerves, while certain other nerves, when active, tend to exhaust the heart and to prevent or hinder its nutrition. Experiments first made on the heart by Gaskell have since been extended to muscles and to other organs, so that the physiology of to-day is largely a question of anabolic and katabolic phenomena. Investigation of the extrinsic cardiac nerves, with their ganglia, shows that although stimulation of the pneumogastric slows the pulse, or strong excitation entirely stops the heart beat, yet on the whole the nerve is a help to the heart; that if in an animal you take a feebly beating heart stimulation of the pneumogastric will, after a time, strengthen the heart. If you take the dying heart of a frog, in which the auricles are still beating, but the beat fails to pass over to the ventricle, by stimulating the pneumogastric you can often get the heart back to its normal rhythm. Often one gets the phenomenon that the auricle in a dying heart makes two beats for the ventricle's one, and finds that on stimulating the pneumogastric one gets the normal beat, one stroke of the auricle corresponding to one stroke of the ventricle; we can therefore on experimental grounds assert that the pneumogastric is essentially a trophic nerve for the heart.

The same observer (Gaskell) had also shown some few years before, that mingled with the motor fibres of an ordinary motor nerve were vaso-dilator fibres, fibres which dilated the arteries of the muscle at the same time that the muscle fibres contracted. One can paralyze the motor fibres proper by curare, and then, on stimulating the nerve trunk, get the vascular dilatation without the muscular contraction; but normally the two things go together. Whenever a muscle contracts, be the impulse that excites the contraction voluntary or reflex, the contraction

is accompanied by an impulse which acts upon the blood-vessels of the muscle and for a time paralyzes the muscular coats, so that its arteries allow more blood to flow through the muscle.

It occurred to me that it would be interesting to investigate this question in connection with the nerves of the heart. We there find the vagus of which I have just spoken; and in addition the accelerator nerves which, when excited, quicken the heart's beat, and may in a sense be called the motor nerves of the heart; though, as is well known, the heart will continue to beat when all influences from outside nerves are cut off from it.

The vagus being the trophic nerve of the heart, it might be readily supposed *a priori* that it would be the nerve which contained the fibres for dilating the coronary arteries. On the other hand we have the analogy of ordinary muscle where we know that the motor nerve branches which excite the organ to activity are those which contain the vaso-dilator nerves fibres.

At the beginning of this session I asked Mr. Lingle to study this problem with me, in the physiological laboratory of the Johns Hopkins University. Our research is still far from complete, but we have, I think, reached some interesting results. Our method has been to anæsthetize the animal, open the thorax (of course starting artificial respiration), and then by opening the pericardium to expose the heart: we then selected some little artery on the surface of the ventricle for careful observation. The best arteries are those that are in the etymological sense of the word capillaries, little arteries just as big as a hair, which one watches through a hand lens. It is quite easy to observe them, but it is not easy always to observe their changes in diameter, but by selecting a little network on the surface of the myocardium and watching attentively, one can usually see any changes that occur in the diameter of its vessels.

We began by stimulating the pneumogastrics, and found that every time that the pneumogastrics were stimulated the arteries of the heart dilated; the heart became distinctly redder and the superficial arteries of the myocardium were very distinctly increased in diameter. Then the query arose which led to the most interesting point in our work.

In order to watch accurately these changing blood-vessels it was necessary to stop the artificial respiration, because the lungs moving up and down, kept heaving the heart up and down. It was hard enough to watch a given vessel during the beat of the heart itself; with the respiratory movements added it was practically impossible. But the cessation

of artificial respiration introduced a new factor; and we therefore tried the effects of stopping the respiration without simultaneously stimulating any nerve. Under these conditions we got *dilatation* of the coronary arteries, though dyspnœa causes constriction of the arteries in every other part of the body.

The diagram I exhibit is taken from a typical experiment. The top line is the chronograph line, each notch being a second. The next is the respiration line. Toward the far end of the diagram there are parts of two respiration curves. At the level of the first vertical line the respiration stopped, the stopcock having been turned which cut the lungs off from the pump, and towards the other end of the tracing respiration commenced again, as is indicated by the curves. The line *C* has one little notch in it. That notch was worked by the observer with a little electric signal and indicated when he saw a change in the blood-vessels of the heart. The lowest line is a tracing of the blood pressure taken in the carotid artery, the beats being of course pulse beats.

The point I want to call attention to is this. You see that for some time after the respiration is stopped there is no rise in the blood pressure, and before there is any rise in the blood pressure the observer signals that he has seen a change in the diameter of the blood-vessels. That change was always an increase. Later on comes the dyspnœic rise of blood pressure and then, artificial respiration being used again, blood pressure returns to the normal.

In our first observations as to the diameter of the cardiac arteries during commencing asphyxia, we thought their dilatation might be due to the fact that there was a general rise of blood pressure, which rise mechanically distended the coronary arteries and their branches; but, as you see, the observer always signals before there is any rise of blood pressure in the carotid; therefore the phenomenon is a true vaso-dilator one. The point of chief interest is that while in commencing suffocation the arteries of the body in general constrict, the arteries of the heart dilate. The heart arteries dilate that the last remaining oxygen shall go to that fundamental vital organ. It is one of the most beautiful preservative mechanism that I know of in the whole physiological working of the body.

X.

THE NORMAL RESPIRATORY MOVEMENTS OF THE FROG, AND THE INFLUENCE UPON ITS RESPIRATORY CENTRE OF STIMULATION OF THE OPTIC LOBES.*

With Plate 12.

[*Journal of Physiology*, Vol. I, 1878. Reprinted in *Studies from the Biological Laboratory of the Johns Hopkins University*, Vol. I, 1879.]

I.

The frog has very frequently been employed by physiologists for investigations concerning the gaseous exchanges of the animal body under various conditions; but there exist remarkably few observations upon the nervous factors of its respiratory mechanism; so that while the mode of action of the respiratory centre of the mammal and the influence of various conditions upon its discharges are tolerably well known, there is an almost complete absence of corresponding knowledge with regard to the frog. It is known that its respiratory centre lies in the medulla oblongata (according to Flourens† well forward opposite the posterior border of the cerebellum), and that parts of the brain in front of this can be removed without causing cessation of the respiratory movements; but beyond this we know almost nothing. v. Helmholtz²⁷ observed that stimulation of the central end of the pneumogastric nerve in the frog brings about cessation of the respiratory movements in that stage which is characterised by retraction of the throat. Heinemann³ found certain respiratory disturbances to follow section of the pneumogastric trunks, but ascribes them to paralysis of muscles of the glottis. Goltz⁵ has shewn that if a frog's back be struck tolerably smartly against some solid object its respiratory movements cease for some time; and also that by irritation of the intestines its respiration is inhibited in the phase during which the external nares are closed, while stimulation of the skin causes cessa-

* The first part of this paper was read before the Maryland Academy of Sciences, Feb. 18, 1878; the second part before the Johns Hopkins University Scientific Association, March 6, 1878.

† See List of Authorities, p. 139.

tion of the respiratory movements with the nares open. Von Wittich⁶ cites experiments on frogs tending to shew that the respiratory centre in them is reflex in character, apnœa occurring after the skin of the animal is removed, even when the blood is extremely venous: he also states that if the lungs be extirpated and the animals therefore limited to cutaneous respiration, they do not exhibit dyspnœa, but all respiratory movements cease and are only called forth by peripheral stimulation: the apnœa he also states to follow section of the vagi. Schiff²⁸ states that very strong induction currents applied to various regions of the body of the frog cause cessation of the respiratory movements in the expiratory state, with the throat relaxed. Strong stimulation in the coccygeal region, however, causes merely cessation of the movements of the nares, while the throat movements persist, but with a slower rhythm. Rosenthal² ascribes these results to unipolar actions on the vagus, etc. This short list of observations, in some cases merely casual, on the influence of extrinsic influences upon the functional activity of the respiratory centre in this animal, includes all that I have succeeded in finding.

The cause of this general neglect I imagine lies mainly in the apparent complexity of the respiratory movements in the frog, which makes it somewhat difficult to arrive at a clear working idea as to the normal mode of action of its respiratory centre. *A priori* the frog would seem extremely well adapted for observations of the kind in question. In the mammal the results of experiment upon influences inhibiting or otherwise affecting the respiratory centre are almost invariably complicated by simultaneous changes in the blood gases (due to interference with the normal respiratory rhythm), altering the stimulus acting upon the centre; or if artificial respiration is employed to overcome this it introduces new complications through the afferent impulses excited in the vagi, by the expansion and contraction of the lungs, influencing the respiratory centre (Breuer²²). In the frog we might expect to be largely freed from such secondary effects. Carrying on, as it does, a large proportion of its respiration through the skin, which, at least in winter frogs, seems perfectly sufficient to keep the blood in a state of normal aëration for a long time, the oxygenation of its blood is much less dependent upon the normal performance of the respiratory movements. In the winter frog, in fact, nature carries on an artificial respiration for us, which has the advantage of being independent of extension or collapse of the lungs. Moreover, its tissues in general, and in this we may expect the respiratory centre to share, shew a much slighter sensitiveness to deficiency of oxygen than

do those of the warm-blooded animal. Wishing to make some experiments upon the influence of parts of the brain in front of the medulla oblongata upon the force and frequency of the discharges of the respiratory centre, I turned my attention in the first place to the frog; influenced partly by the above considerations and partly by the ease with which operations upon its encephalon can be performed, and the rapidity and completeness with which the animal recovers from them.

It was in the first place essential to obtain a definite knowledge of the normal method of the frog's respiration as a preliminary step towards a knowledge of the working of its respiratory centre. This was the more important on account of the double character of the frog's respiratory movements, in some of which, as is well known, only throat muscles are concerned, while others are characterised by co-operation of muscles of the trunk; a doubleness which made it possible that the mode of action of its respiratory centre was essentially different from that of the mammal. When I turned to the literature of the subject I found that the statements on the subject were either too vague to be of use, in such treatises as that of Milne-Edwards²⁴ no notice being taken of the two kinds of respiratory movements; or that the statements made in the more detailed accounts of various observers differed in essential points. It became therefore necessary to investigate the matter afresh, and if possible by improved methods.

The physiologists of the end of the 17th and of the 18th centuries did not fail to observe that there was an essential difference in the mode of respiration of the frog and of the mammal; what chiefly attracted their notice being the fact that while the lungs of the latter collapsed when the chest was opened, those of the frog remained dilated, or if at first collapsed could be subsequently distended by the animal. Swammerdam,⁷ Malpighi,⁸ Morgagni,⁹ and Laurenti¹⁰ all refer to one or other of these facts, and give essentially correct accounts of the respiratory mechanism. On the other hand, Brémond¹¹ and Blumenbach¹² ascribed this faculty of remaining distended when exposed to the air to some specific power inherent in the frog's lung. Brémond's account is curious, for he admits in one part of his treatise that Malpighi's account of the mode of respiration in the frog is correct, but fails to see how this can account for the distension of the lungs when the visceral cavity is opened. He therefore concludes that fleshy fibres, which he has seen in the dried lung, are the cause of its dilatation during life, and points out that "*ces fibres doivent avoir beaucoup de force dans ce viscère et servir également quoique d'une*

façon différente pour sa contraction et sa dilatation"; a sort of anticipation of the "active dilatation" of muscular fibres spoken of by some physiologists as occurring in arterial walls. The first detailed account of the mode of respiration of the frog was however given by Townson¹³ in 1794: his account far excels in minuteness of description those of any of his predecessors, and is substantially correct in all points. He describes not only the mechanism by which air is driven into the lungs, but also the mode of its expulsion by the contractility of the distended lungs, and the co-operation of the muscles of the wall of the visceral cavity. He pointed out that all the throat movements were not alike, but that some of them differed in character from the rest, and were alone accompanied with closure of the external nares and contraction of the flank muscles. He also described and figured the muscles of the throat, and first shewed that if the mouth of a frog was kept open it could not send air into its lungs, an experiment which Milne-Edwards erroneously states to have been first performed by Herhold.¹⁴ The views put forward by Townson have been since generally accepted, but Rudolphi,¹⁵ and subsequently Haro,¹⁶ gave an essentially different account of the respiratory mechanism of the frog by which it is assimilated to the mode of respiration in birds; the throat movements according to Haro being a mere freak of nature intended to conceal the actual process. The latter he states to consist in a compression of the lungs by an indrawing of the posterior end of the sternum due to contraction of the sternohyoid muscles which are attached to it. By this contraction air is driven out of the lungs, and so expiration is brought about: when the muscles relax the xiphoid cartilage by its elasticity returns to its former position, and dilates the cavity in which the lungs lie; consequently air enters and expands them. Inspiration is also in a subsidiary degree dependent upon the ascent of the hyoid carrying with it the glottis and trachea: by this the anterior parts of the lung sacs are expanded so that air passes into them. The experiments by which he attempts to prove the correctness of his statements are, however, of a highly inconclusive character, amounting to little more than the observation that the respiratory movements continue when an opening is made in the floor of the frog's mouth, a continuance which he considers to prove that actual functional respiration was performed: air enters the lungs since expiration occurs as ordinarily, "ce que prouvent les contractions de l'abdomen et des flancs." This is of course equivalent to saying that a mammal can breathe when its thorax is opened, because one sees the respiratory movements of the ribs and diaphragm to continue. The

further proofs offered by him are of little more cogency, consisting in the fact that a frog treated as above and with its visceral cavity opened may live several days; and that when the animal's mouth was held open the currents of air could be felt passing out from the glottis when the sterno-hyoid muscles contracted. By this latter statement, which at first sight might seem to prove the existence of some such respiratory mechanism as he describes, it seems clear that he only refers to the expulsion of air which might already be contained in the lungs when the observation commenced, for he says the best way of seeing it is to hold the animal under water and see the bubbles rise: under such circumstances there could be no question of an entry of fresh air into the lungs. Direct observation of the lungs, when the floor of the animal's mouth was removed, shewed him a "sensible" dilatation of the anterior parts of those sacs during the period at which he supposed inspiration to be taking place, while their posterior extremities showed no dilatation. He speaks of the changes in the diameters of the chest wall, which he considers the essential part of the respiratory mechanism, as not being sensible: such feeble movements as these are, in his opinion, the actual respiratory movements of the frog; the obvious movements of throat and flank being of little or no significance. Panizza,¹⁷ incited by Haro's statements, undertook an experimental investigation of the question, and while confirming Haro as regards Chelonians, proved very clearly that his account of the respiratory mechanism of the frog was erroneous, the agents which he regarded as the sole ones being at the most quite subsidiary. Panizza removed the skin from behind the fore limbs of the frog, and was thus able to watch the lungs through the thin muscular wall of the visceral cavity. He was then able to see that they dilated and contracted considerably when the throat and nares were left intact; but that when the floor of the mouth was removed, as described by Haro, or when the outer border of the nostril was cut away, so as to prevent its closure, then the lungs soon collapsed; and during the inspiratory movements dilated extremely little, and only at their anterior part. When a tympanic membrane was removed the lungs similarly collapsed; but if the opening were closed by the finger they were soon dilated, and the dilatations could be seen to occur at the moments of retraction of the throat. All these phenomena were quite irreconcilable with Haro's view of the respiratory mechanism, and proved conclusively that the older view was in the main the correct one, even if some such action as Haro imagined occurred in extreme dyspnoea. Panizza also shewed that if a

frog's glottis were hermetically closed the animal could live in a room at 7° to 8° for twenty-one days; so that the fact that Haro's frogs lived some five or six days did not in the least prove the occurrence in them of any active lung respiration. The insufficiency of continued vitality as a proof of pulmonary respiration in the frog had also been shewn previously by the experiments of W. Edwards.³⁰ Panizza also observed, as Swammerdam¹⁸ and Townson¹³ had previously done, that the frog sometimes diminishes its mouth cavity in order to drive air into its lungs, not only by retracting the throat but by drawing in the eyeballs. Heinemann³ seems to have been the next to take up the question with thoroughness, and his article is extremely good. Accepting Townson's account in the main, he supplements it in various points, the more important of which are as follows. The contraction of the flank muscles (which, as Townson pointed out, only accompanies the more powerful throat movements) follows the descent of the throat, occurring at the moment when it again begins to ascend. With the smaller throat movements the abdominal walls shew slight variations which are brought about by changes of place in the hyoid. The glottis is closed during descent of the hyoid; immediately after the ascent commences it opens widely, to close again when the throat reaches its highest position. The exact discrimination is however not easy, and can only be attained after numerous experiments, since decapitated frogs on which these observations were made, commonly breathe differently from normal frogs. If the brain be almost completely removed (with the fore part of the head so as to expose the glottis) the frog sits for some time, often many minutes, without movements of the throat: when these recommence they are usually all of the more energetic type, and then always accompanied with opening of the entrance to the larynx. In a few cases, however, the feebler movements are seen, and during these the larynx remains closed. He points out the great differences seen in frogs as to the ratio in number of the more feeble to the more powerful respirations in a given time: the latter, which alone he calls respirations, may occur only once in 2-3 minutes, but may on the other hand rise from 66-104 in one minute, the latter when both vagi are cut. The more feeble throat movements he thinks may be explained by supposing that the impulses starting from the medulla oblongata must have a certain strength in order to call forth the whole series of respiratory movements. The throat muscles might be set in work without simultaneous stimulation of the glottidean muscles; which latter first occurs when the stimulation at the centre has reached a certain height. Expulsion of air from

the lungs immediately precedes its entry, so that the movements causing the two are almost continuous. As will be seen presently, my own observations have led me to differ from Heinemann as to the relationship in time of the throat movements and the contraction of the flank muscles: simultaneous tracings from throat and flank shewing that the flank contracts at the end of the descent of the throat, and not at the beginning of the ascent. If this be so, he is also slightly in error as to the time of opening of the *aditus laryngis*, which he says is difficult of discrimination; the opening for the expulsion of air must first occur, when the lungs are compressed by the flank muscles, and therefore before the ascent of the throat.

Bert,¹⁹ so far as I have been able to find, was the first to apply the graphic method to the study of the respiratory movements of the frog, but a critical examination of his experiments shows that they are not entirely satisfactory. He makes no reference to the distinction between the two types of respiratory movements, so that it is not always possible to say whether his tracings are those of respiratory movements accompanied by closure of the nares and contraction of the flank-muscles, or whether they are derived from respiratory movements not so accompanied. In his figure 1 for instance, in the *Journ. de l'Anat. et Phys.* (Fig. 52 in his book²⁹) all the respiratory curves are alike, and must all be due to the same kind of respirations. The tracing was obtained by placing a tight-fitting bag, connected with a Marey's tambour, over the frog's nose, and so recording the passage of air into or out of the nostrils. Now if a frog be placed in a small beaker (to exclude external air currents), and when it is breathing quietly a small flock of cotton-wool be held above and a little to the outside of one nostril, the wool will be seen to be blown about by the air expelled from the nares during each kind of respiratory movements. But there is no comparison between the violence with which it is blown in the two cases, its movements being much greater when the flanks contract. From this obvious difference in the force with which the air is expelled it is impossible to conceive that the tracings derived from the tambour should be the same in the two cases, and we have to decide which of the two alone is depicted in Bert's figure. From the letterpress it is clear that the respirations accompanied by flank-contraction are those from which the tracing was taken; and such an uninterrupted series of them only occurs in dyspnoëic or otherwise abnormal conditions. Bert's statement, originally made by Panizza, that normally the frog when driving air into its lungs does not completely close its

nares either externally or internally, but merely narrows them, is probably correct, though his further statement that the animal can under no circumstances do so, seems inconsistent with one of Panizza's experiments. The latter observer found that if the head of a living frog was held immersed in a solution of potassic ferrocyanide for some minutes and then removed, the mouth carefully opened and solution of ferric chloride applied to the internal nares, no blue color was developed. Another of Bert's experiments devised to shew that Haro's views were incorrect is unsatisfactory. He put a tightly-fitting cannula containing liquid (or as described in his book, connected with a recording tambour) in the glottis of a frog, and saw no changes of level in the fluid or movements of the lever: this he ascribes to the mouth being held open by the cannula or to the air being, in other cases, able to pass out through the opening in the pharynx made for the introduction of the instrument, and he concludes that no such inspiratory mechanism as that described by Haro could in this case be active. But here he can only have been dealing with the more feeble respiratory movements, the flank respiratory movements being probably inhibited by the sensory stimulus caused by the tube in the glottis: for if the flank muscles had contracted, thereby compressing the lungs, they must have caused changes in the level of the liquid or in the lever. He states, however, that when the lungs are previously extremely collapsed slight changes in the level do occur, from which he concludes that the mode of respiration described by Haro has, in these conditions, a certain amount of efficacy. Similar objections apply to Bert's second figure (Fig. 53 in his book): this figure gives simultaneous tracings of the changes of pressure in tambours connected by cannulæ, one with a nostril and the other with the cavity of one lung. Here again all the curves are similar, with one slight exception, to which he makes no reference, and which is probably accidental. The changes of pressure in the lungs are, moreover, so trivial, compared with those in the mouth, as to make it almost certain that the glottis was closed during the whole time; the respiratory movements being all of the feebler type; and such slight variations of lung-pressure as did occur, being due to a stretching of the anterior part of the lung by the ascent of the hyoid, in the manner pointed out by Heinemann. Although Bert's experiments are not conclusive, his statements as to the mode of respiration of the frog are, nevertheless, in the main, correct, with the exception of his omission to point out the two degrees of respiratory movements which normally occur. In one point,

he is, I think, more correct than Heinemann, viz., in stating that air passes out of the lungs immediately before the commencement of the retraction of the throat. In his table shewing the conditions of nares, throat, glottis and lungs, during the phases of a respiratory period, it is significant that no mention is made of the abdominal walls; an omission which goes to confirm the suspicion that his plan of introducing cannulæ into the glottis inhibits the more powerful expiratory discharges.

Burdon Sanderson²⁰ has also described the respiratory mechanism of the frog, and given a figure of the curves—obtained from a tambour connected with a cannula placed in one nostril. The curves obtained by him shew marked differences corresponding with the feebler and more powerful respiratory movements, which makes it quite clear that Bert was dealing with only one kind. Sanderson's description of his figure does not, however, so far as I can make out, agree with the figure itself: and his statement that the entry of air into the lungs immediately precedes its expulsion, so that it remains a very short time in those cavities, is at variance with the statements of all other observers and with the results of my own experiments. He states that the contraction of the flank muscles immediately follows closure of the nares and occurs while the hyoid is still drawn upwards. He makes this statement, partly on the ground of direct simultaneous observation of the movements, which is however very difficult to carry out, and partly on the study of the intra-pulmonic pressure: and it is this latter which I think has misled him. He takes the sudden rise of intra-pulmonic pressure to indicate the entry of air into the lungs: it is, I believe, rather due to the compression of the lungs by the flank muscles, the glottis being passively closed. Immediately afterwards, the glottis is actively held open, and the flank muscles having relaxed, air enters the lungs under a less pressure than that at which it was driven out of them. Townson's observation that one lung only may be collapsed in correspondence with a contraction of the muscles of only one flank seems to prove that the glottis is not actively held open during contraction of the flank muscles, for if such were the case, both the distended lungs would almost certainly collapse, the abdominal walls being so flexible.

Whatever be the explanation, simultaneous tracings of throat and flank movements shew that the flank muscles contract, expelling air from the lungs, when the throat is still protruded by descent of the hyoid: that the lungs are distended immediately after this contraction; and the air remains in them a considerable time, viz. until the next flank contraction.

In giving an account of the statements of Heinemann, Bert, and Sanderson, I have anticipated somewhat in criticising them; it now remains for me to give the details of the experiments upon which the criticisms which I have ventured to make are founded. The preceding abstract of the history of the investigation of the respiratory mechanism of the frog shews that while tolerable unanimity upon its broad features has been reached there is still a great discrepancy upon points of detail, and points of which it was essential for my purpose that I should have a clear idea. This was especially the case as regards the time relationships of the throat and flank movements. While it was pretty definitely settled that the minor throat movements sent no air into the lungs as the larger did, and that the flank movements and those of the nares accompanied only the larger, there was a wide difference of opinion as to when these flank movements occurred. Heinemann says they take place at the commencement of the throat retraction; Sanderson, if I interpret correctly his phrase, "while the hyoid is still drawn upwards," at the end of the period of throat retraction; and Bert, at the end of the phase of throat protrusion. If the statements of Heinemann or Sanderson were correct, the discrimination of inspiratory and expiratory discharges from the respiratory centre of the frog became very difficult; for the throat retraction, essentially an inspiratory movement, would coincide in part with the essentially expiratory movement of contraction of the muscles of the abdominal wall. The discharges of the inspiratory and expiratory centres would, in other words, overlap; and for my purpose it was necessary to discriminate them. If it did turn out that the discharges of the two centres could, in part, coincide, that fact in itself would be of great importance. Some of the movements in question being extremely rapid, and the time differences involved extremely small, it was essential to record them simultaneously, and extremely desirable to do so with the frog breathing as much as possible in a natural manner, and if possible in its normal position. For the latter reason I rejected the employment of tambours which necessitated interference with the movements of the nares, and the opening of a lung, and which had besides led to discrepant results in the hands of Bert and Sanderson, and attempted to register the movements of throat and flank directly. At first I did not hope to be able to record in this way the respiratory movements of the unconfined and uninjured frog, and I therefore employed animals whose cerebral hemispheres had been removed. I have, however, recently succeeded in getting tracings of the throat movements in the

uninjured frog sitting free in its natural position, and the complete similarity even in the small details of the two tracings leaves no room for doubt that the whole respiratory movements in the frog with and in that without the cerebral hemispheres are the same: a conclusion which direct observation fully confirms.

The throat tracings were obtained by means of a light lever, which was almost equipoised so as to exert only enough pressure upon the throat to ensure that it followed the movements of the latter. The writing-point of this lever, made of aluminum foil, traced upon the smoked surface of an ordinary revolving cylinder. The lever itself did not rest directly upon the throat of the frog: I found this caused too much irritation so that the animal either jumped away or pushed off the lever before a tracing could be taken; and it had the further disadvantage that the ramus of the jaw sometimes prevented the lever from following the throat when the latter was in extreme retraction. To obviate these disadvantages I fastened a small piece of cork to the lever near its fulcrum; into this a pin was stuck in a horizontal position; the free end of this pin carried another piece of cork and into this was inserted the point of another pin which was placed in a vertical position, and the head of which pressed gently on the frog's throat; and so any movement of the latter was transmitted to the lever. If the pin-head be very gently brought in contact with the throat (which in my apparatus was done by a rack and pinion movement) an uninjured frog will frequently bear the contact, and give a tracing for more than half a minute.* Frogs whose cerebral hemispheres are removed are frequently very troublesome at first, jumping away the moment the apparatus touches them; but when once they have borne the lever for a short time they usually give little trouble afterwards, seeming to get used to it; and when they do move they commonly either merely push the lever away with one foot or turn aside from it instead of jumping away. I have found it a great help to make use of Tarchanow's²⁶ observation that compression of the abdominal cavity lowers the reflex irritability of the frog: if the animal be seized between the finger and thumb just in front of the urostyle and gently squeezed it will usually stay where it is placed, and the lever can be adjusted before it again gets irritable: this pressure nearly always

* My tracings from the uninjured frog were obtained in midwinter, and the frogs had probably not quite their normal irritability. They had however been for several days in a room at a temperature of from 15° to 18° C. and were vigorous and lively, jumping with great activity when irritated.

leads to complete cessation of the respiratory movements for some seconds after it is removed, and this also facilitates the adjustment of the lever. When the animal wakes up again and begins to breathe, it commonly takes no notice of the lever for many minutes. None of my tracings was taken until at least a minute had elapsed after the resumption of the respiratory movements, so as to eliminate any possible effects of the previous cessation, or pressure.

The frogs which I have employed were nearly all partly-grown specimens of *Rana lentiginosus*, about the size of full-grown specimens of *Rana temporaria*. The animal was placed on a sheet of lead which formed a slightly inclined platform in a trough filled with water. The highest edge of this platform was in contact with one end of the trough and level with it; over this end of the trough the throat of the animal projected and had the pin-head of the lever apparatus in contact with it; while in consequence of the slope of the platform the posterior limbs and body of the animal were partly immersed in the water. A thermometer in the latter was used to indicate if any considerable changes in the temperature of the room occurred during the more prolonged experiments; as the force and frequency of the frog's respiratory movements are subject to great changes with alterations of temperature; wherever temperatures are given in the details of the following experiments they are those indicated by this thermometer.

Figures 2 and 3, Plate VI [Plate 12 of this volume], give tracings of the throat movements of the uninjured frog as obtained in the manner just stated: Figure 4 is a similar tracing from the frog with its cerebral hemispheres removed; and it will be seen that it is identical in character with those obtained from the normal animal. In these tracings, ascents of the curve indicate throat retractions, and descents, throat protrusions; and it will be seen that at somewhat irregular periods there occur more marked protrusions followed by more powerful and sudden retractions: these are the throat signs of those respirations which are accompanied with the closure of the external nares and the active contractions of the flank muscles: and the first point was to decide in what relation these three events stood to one another. As to the contraction of the nares there can be no doubt that it accompanies the more powerful throat retractions. There is considerable difficulty in observing simultaneously the nares and the throat, but it is much more easy to watch at the same time the lever and the nares, and this indicates the relationship just stated; which is moreover that universally accepted, the occlusion of the

nares simultaneously with the more powerful protrusions of the throat being *a priori* extremely improbable. For it is agreed by all observers since Haro that it is during the marked throat retractions that air is driven into the lungs of the frog. The main point then which I had to determine, was the relationship in time of the various phases of the throat movements to the contractions of the flank muscles; a point on which Heinemann, Bert, and Sanderson differed. With this object I placed a second rectangular lever, so that its short vertical limb was in contact with the frog's flank, while its longer horizontal limb wrote on the revolving cylinder, immediately over the throat lever. The tracings thus obtained shew conclusively that the flank contraction immediately precedes in each case the powerful throat retraction, being in fact contemporaneous with the powerful throat protrusion; or rather with that part of it which is characterized in Figures 2, 3 and 4, at the points *a*, by a more sudden descent of the lever. Figures 6 and 7 represent such simultaneous tracings, and it will be seen that the flank contractions indicated by the descents *b* in the upper tracing of each figure immediately precede the powerful throat retractions *c*, by which air is driven into the lungs. The tracings further shew that from this time the lungs remain filled, as indicated by the continued protrusion of the flanks, until the next active flank contraction, so that the air, far from remaining a brief time in them, stays there for a considerable period. Otherwise we should have collapse of the lungs attended with protrusion of the flexible walls of the cavity containing them. The air therefore enters the lungs immediately after its expulsion by the flank muscles, and not immediately before it, as stated by Sanderson. The minor curves, *d*, described by the flank lever during the minor throat movements, have nothing to do with an entry of air into the lungs or its exit from them, as I shall shew presently. The break in the ascent of the lever at *f* while air is entering the lungs is due to its inertia. Heinemann also must be wrong in stating that the glottis only opens when the throat commences one of its more powerful retractions. It must open just before this when the flank muscles contract; but probably this opening is passive and inconspicuous as compared with the active inspiratory dilatation of the glottis which succeeds it.

The tracings from which Figures 6 and 7 are copied were, it is true, obtained from frogs whose cerebral hemispheres were removed; but the exact agreement of the throat movements in such frogs with those of uninjured frogs makes it impossible to believe that their normal respira-

tory *modus* has been altered. Certainly not to the extent of reversing the usual time relationships of the throat and flank movements.

In the tracings it will be noticed that the ratio of the number of the major to the minor throat movements is subject to considerable variation. In Fig. 6, after a period without major throat movements or flank contractions, a number occur close together; and the inspiratory effect on the whole overbalances the expiratory, the lungs becoming more and more distended, as shown by the gradual ascent of the upper tracing. In Fig. 7 we find a powerful emptying of the lungs following one of these periods of dilatation and then no active flank contraction again for a considerable time. Such a grouping of major throat movements as is shown in Fig. 6 is unusual. In Fig. 5, taken from an uninjured frog of a different species (which I have not been able to determine), the rhythm is very regular, and the major throat movements are unusually numerous; whether this is an individual or a specific characteristic I do not know; it probably represents a somewhat dyspnoëic condition.

I have gone with this detail into the account of the frog's respiratory movements because those of the throat being by far the most easily recorded it is of great advantage to be able, if possible, to interpret tracings from the throat so as to be able to read from them what is happening at the same time in nares, flanks, and lungs. If I am right in the conclusions above stated, it will be seen that this is not only possible but easy. In Figs. 2, 3, 4 and 5 the smaller curves, *g*, will indicate throat movements unaccompanied by closure of the nares or by any change in the volume of air in the lungs, but simply renewing the air in the mouth. The more marked protrusions of the throat, *e*, on the other hand, will be accompanied towards their termination at the points marked *a* (usually differentiated by a sudden alteration in the curve, but sometimes appearing merely as a prolongation of the period of protrusion, as is well seen in Fig. 6) by active contraction of the flank muscles and the expulsion of air from the lungs. The powerful throat retraction following this is accompanied (at any rate in its earlier part) by more or less complete closure of the nares, the entry of air into the lungs, and passive protrusion of the flanks: from that time the lungs remain distended during the succeeding smaller throat movements until the next powerful throat protrusion is accompanied again with flank retraction and expulsion of the air. To facilitate description I shall in future designate the respirations indicated by the smaller throat movements simply as "throat respirations," and those accompanied with the change of air

in the lungs as "flank respirations," though of course the throat shares in these latter also.

There were two other points on which it was desirable to obtain tracings. Heinemann has pointed out that if the frog's flank be very carefully watched, movements in it will be seen to take place even during the "throat" respirations. These he ascribes as above stated, not to an entry or exit of air from the lungs or to active contractions of the flank muscles, but to an increase of the pleuro-peritoneal cavity in its antero-posterior diameter by the ascent of the hyoidean apparatus, which increase is compensated for by a diminution in the transverse diameter; the contents of the cavity remaining the same and no air entering or leaving the lungs. If this be so, the throat retracting and pulling the lungs up out of the visceral cavity, without at the same time dilating them, as happens in the throat retraction period of the "flank" respirations, then the flanks ought to shrink when the throat is retracted in these "throat" respirations. Simultaneous tracings of throat and flank during the "throat" respirations (Fig. 1) shew this to be the case. The upper tracing is from the flank; ascents in it represent flank protrusions: the lower tracing is from the throat; descents in it, as before, indicate throat protrusions. It will be seen that when the throat protrudes the flank protrudes, and *vice versa*; exactly the reverse of what occurs in the "flank" respirations. Heinemann's explanation of these slight passive flank movements is therefore the correct one. In this way the minor flank movements *d*, in Figures 6 and 7, above referred to, are produced. These movements must not, however, be confounded with feebly active flank movements which occur in certain dyspnœic states with each throat movement. In such cases these active flank contractions are readily differentiated by their suddenness. It will be noticed in Figure 1 that a considerable series of "throat" respirations occurred, uninterrupted by any "flank" respiration: a phenomenon to which several observers have referred.

Finally it remained to be seen whether there was any fragment of truth in Haro's view of the frog's respiratory mechanism: Panizza, Bert and others thinking that possibly some such action as he describes may occur as a subsidiary phenomenon, at any rate in dyspnœic states. To investigate this I fastened an uninjured frog upon its back by strings passed around its limbs, and recorded by levers simultaneously the throat movements, and those, if any, of the posterior end of the sternum; in some cases the flank movements were also recorded. Such tracings

shewed that at the time of active contraction of the flank muscles (expiration) the lower end of the sternum was slightly pulled inwards towards the vertebral column: on account of its elasticity, this end will no doubt tend to return to its position of equilibrium when the expiratory muscles relax, and so will passively tend to bring about an inspiration by dilating the chamber in which the lungs lie. The amount of this influence must however be very small; and it is open to doubt whether the inbending of the sternal end is not due rather to the contraction of the expiratory muscles in the abdominal wall than to the sterno-hyoids: especially as Heinemann could see no change in the position of the posterior end of the sternum, to be brought about by tetanising the latter muscles. In extreme dyspnœa these movements of the posterior end of the sternum become considerable.

Such being the normal respiratory movements of the frog, it became my next object to gain some idea if possible of the relationship in which the activity of the respiratory centre in this animal, as indicated by its respiratory movements, stood to that of the mammal, with its rhythmic inspiratory and expiratory discharges, innervating different groups of muscles. The muscles concerned are of course widely different in the two cases; but that in itself gives no reason to conclude that the fundamental working of the respiratory centres should not be the same in both. At first sight however the frog's respiration seems to be essentially different: it looks as if we had in it to deal with two distinct respiratory centres, each with its inspiratory and expiratory division, and concerned respectively with the "throat" and "flank respirations," which seem to have a rhythm quite independent of one another. The centre for the "flank respirations" would then be characterised by the greater violence of its discharges and their less frequency, as well as by their radiation to muscles not under the influence of the other centre. The fact, however, that under certain conditions, as dyspnœa and, as I shall shew presently, of excitement of the optic lobes, the flank and throat respirations gradually shade off into one another, is against the hypothesis of two totally independent centres; and I think the whole mechanism can be explained by the working of a single inspiratory and a single expiratory centre, and without doing violence to what is known concerning the mode of action of those centres in the mammalia. That we have to do with only a single respiratory centre, with its inspiratory and expiratory divisions, is the view adopted by Heinemann, as quoted above. His attempt to

account for the different amounts of the discharge in the two cases is however not satisfactory. He supposes that the stimulus acting upon the centre is at first only powerful enough to cause discharges which radiate to the throat muscles. These bring no air into the lungs; the stimulus to the centre therefore increases and causes finally a discharge which radiates to more muscles, causing what I have called a "flank" respiration and renewing the air in the lungs. But if this were the whole matter, then the throat respirations ought gradually to increase in strength and in the number of muscles concerned; until the last of the series passes into a "flank" respiration; and this my tracings shew is not the case. In the normally breathing frog there is no transition, but a sudden jump from one to the other.

If the brain and spinal cord of a frog be destroyed and the animal be then held in its natural position, it will be seen that the throat assumes the protruded state: so that this is its position of equilibrium in the normal posture of the animal; and that to which it will return when muscles which have removed it relax. This protrusion is sometimes not quite so great as that which corresponds to the position of the throat in the protrusion phases of the "throat respirations"; but in such cases it will be found that, as is commonly the case, the lungs have been entirely emptied of air during the operation; so that instead of being moderately distended as is their condition during the normal "throat respirations," they are now in a state of extreme collapse, indicated by the abnormal retraction of the abdominal walls. In this general retraction of the soft boundaries of the body cavity the throat shares somewhat; and moreover the larynx is probably pushed out somewhat, in normal conditions, by the distended lung, and this influence also is now entirely removed. In fact if in such cases the lungs be moderately distended by blowing air through the glottis, and the animal be then held again belly downwards, it will be seen that its throat assumes a position of protrusion quite as great as that which occurs in the "throat respirations." We may conclude that in these respirations we have only to do with discharges of an inspiratory centre, leading to contractions of the elevators of the hyoid apparatus; the throat protrusions being passive. These respirations will answer closely to those which take place in the normal breathing of many mammals, where the expirations are passive; and in the frog, as in them, we shall have a more irritable or a more readily discharging inspiratory centre, and a less irritable or less readily discharging expiratory centre.*

* See Lockenberg²¹.

If the stimulus to the inspiratory centre was gradually increasing while the series of throat movements went on, one of two things must happen: either the throat movements would increase gradually in extent, or they would more probably (the resistance to the discharge remaining the same) become more frequent; but they do neither. This can be seen in Figs. 2, 3 and 4, and especially well in Fig. 1, where we have a long series of uninterrupted throat movements, and shews how efficient in winter frogs the skin respiration is, serving to keep the stimulus to the respiratory centre constant for a long time. When the throat respirations have gone on for a time, which is subject to considerable variation, the stimulus which has meanwhile been acting also upon the expiratory centre finally attains a degree which arouses that centre to discharge; and the result is an active expiration with contraction of the flank muscles, and usually of the depressors of the hyoidean apparatus; as is shewn by that protrusion of the throat beyond its position of equilibrium which is indicated by the greater descent of the curves in Figures 2, 3, 4 and 5 at the points marked *a*. Sometimes however the discharge does not radiate to these muscles, and the activity of the expiratory centre then is only indicated on the tracings obtained from the throat by a prolongation of the period of protrusion. This is well seen in Figure 6 at *a*, and characterises certain frogs throughout. A more difficult question now arises: how to account for the greater contraction of the elevators of the hyoid in the immediately following inspiration, and the radiation of the discharge to the muscles of the nares and glottis, without calling in the aid of an inspiratory centre different from that which brings about the ordinary throat retractions; or without assuming some special stimulus acting upon the inspiratory centre at this moment, and corresponding to nothing which occurs in the mammal? The answer which I venture to propose to this question is the following. In the first place it will be noted on the tracings that the interval between this inspiration and that which preceded it is always longer than the interval which separates the inspirations of the "throat respirations" from one another; the activity of the expiratory centre has apparently inhibited the inspiratory centre, or increased the resistance to its discharge; and the normal stimulus thus acting longer upon the centre would be apt to cause an unusually powerful discharge when the inhibiting influence or the increased resistance was removed (Rosenthal,² p. 246). That the unusually excited centre should not only stimulate to more vigorous contraction the muscles which it usually affects, but should radiate

impulses to others, is only in accordance with what we know of its activity in other cases. The experiments of Breuer,²² confirmed by Lockenberg,²¹ have moreover shewn that contraction of the lungs, acting through certain fibres of the vagus, facilitates inspiratory discharges in the mammal; and if we suppose this to be true of the frog also, we should expect a more vigorous inspiratory discharge to follow the active expiration with its attendant collapse of the lungs; this latter probable influence needs, however, experimental confirmation for the frog; and this I have not yet had the opportunity to undertake. But in one or both of the above agencies we have, I believe, a sufficient explanation of the more powerful inspiratory discharges of the "flank respirations."

It will be seen that in the above I have spoken of the centre which innervates the elevators of the hyoid as an inspiratory centre throughout, although the majority of its discharges lead to no entry of air into the lungs. If however this centre is, as I believe, the same as that which from time to time does bring about the propulsion of air into the lungs, the only difference being that in some cases its discharge radiates more widely than in others, and affects new muscles, it is undesirable to give it two names; it is the inspiratory centre, although sometimes its activity drives air out of the mouth, not into the lungs but to the exterior of the body. This frequent renewal of the air in the mouth cavity will lead to its being nearly as pure as the external air; when the active expiration takes place and the lungs are emptied, some of this pure air must be left in the mouth, and, in the immediately succeeding inspiration, will be sent into the lungs as a sort of "tidal air" with some of the air just expelled from them, which will correspond to the "stationary air" of the mammal. The considerable time that the inspired air commonly remains in the lungs is probably correlated with the simplicity of their structure. Almost simple sacs, little impediment is in them opposed to the renewal by gaseous diffusion of the layer of air in contact with their inner surfaces; and so there is not the need for that promotion of the mixture of the layers of air by frequent mechanical movements which is requisite in the complexly subdivided mammalian lung. Moreover the large cavity of the lungs in comparison to the surface in which the capillaries lie renders the frequent renewal of the air unnecessary.

The fact that many respiratory movements in the adult frog have no immediate connection with the renewal of the air in the lungs has a special interest, for it seems probable that it is a physiological remnant of the frog's larval and ancestral mode of respiration. The tadpole pos-

sesses, for a time, and ancestors of the frog possessed probably throughout their whole life, both lungs and gills; while immersed, water must be driven over the surface of the gills by contractions of the mouth cavity; and it is of course important that this water should not at the same time be sent into the lungs, so the dilators of the glottis must not be stimulated. This renewal of the water will then be due to movements answering to those which I have called "throat respirations." Finally when the nares come to open into the mouth and the gill openings close up, these movements remain; but they now drive air out through the nostrils instead of water through the gill chambers, and so without any sudden change in its nerve centres, which otherwise would seem unavoidable, the frog becomes an entirely air-breathing animal, except such respiration as may be carried on by its skin while under water. While the gill openings remain, if the animal is to inflate its lungs with air, there must be a means of closing these openings; and Martin-Saint-Ange²³ has shewn that a very complete apparatus for such closure exists in the tadpole of the salamander. In the frog's tadpole this apparatus is less complete, but from the more enclosed condition of the gills he thinks it is efficient in this case also. If the common statement be correct, that frog tadpoles frequently require to come to the surface to breathe in the later stages of their development (but while still possessing functional gills), the apparatus for closing the gill clefts, or the gill sac, must in fact be efficient. Otherwise I should be inclined from Martin-Saint-Ange's description to doubt the functional utility of the closing apparatus in these tadpoles.

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II.

Having in the manner above described attained at least a working hypothesis as to the normal mode of action of the respiratory centre in the frog, I was able to set to work with more definiteness on the investigations of influences altering its functional activity; and first I turned my attention to the influence of stimulation of the *corpora bigemina*, the so-called "optic lobes." Even in the mammal very little is known concerning the influence of parts of the brain in front of the *medulla oblongata* upon the respiratory rhythm. It is known of course that respiratory movements persist in some fashion when all these parts are removed: and that the will, whose manifestations are correlated with the integrity of some of them, is capable, within limits, of governing the discharges of the respiratory centre. The influence of sensory stimuli is also known to act through the mediation of the cerebral hemispheres; and according to Rosenthal¹ the inspiration-inhibiting influence of the recurrent laryngeal nerve, first demonstrated by Burkhart,² is exerted similarly. Danilewsky³ states that removal of the cerebral hemispheres in the mammal makes the respiration slower but more energetic, the inspiratory movements becoming more powerful. During the last few years also various observers have found alteration in the respiratory rhythm to accompany electrical stimulation of various localities in the anterior portions of the brain. Thus Danilewsky³ found the respiratory movements of dogs and cats slowed with an initial deeper inspiration by stimulation of the cauda of the corpus striatum. Stimulation of medium strength brought about a deep inspiration, followed by a slow expiration, and then complete cessation of the respiratory movements, which often lasted longer than the stimulation. He saw the same results follow stimulation of the "facial centre," though he is in doubt whether in the latter case the result was not due to escape of the current to deeper parts: he also found that stimulation of the corpus striatum caused cessation of a quickening of the respiratory movements brought about by stimulation of the tibial nerve. Ferrier⁷ states, erroneously, that Danilewsky had found electrical irritation of the interior of the *corpora quadrigemina* to cause a deep inspiration, followed by prolonged and powerful expiratory efforts, and had in this anticipated results obtained by Lauder Brunton and himself. From this I conclude that Brunton and Ferrier have found these results to follow stimulation of the *corpora quadrigemina*. Balogh⁴ found that stimulation of certain convolutions

and of the posterior part of the corpus striatum caused more frequent respirations; while stimulation of parts of the supersylvian fold caused cessation of the movements.

As already stated, Flourens has shewn that the respiratory centre of the frog lies well forward in the medulla opposite the posterior edge of the small cerebellum. The comparison of tracings such as that represented in Fig. 4, of which I have many, with the tracings taken similarly from the normal frog, shews that the removal of cerebral hemispheres and optic thalami in this animal produces no alteration in the respiratory movements: unless perhaps a slight tendency to greater regularity in the ratio of "throat" to "flank" respirations in a given time. When the optic lobes are removed, I am inclined to believe that the respiration is affected, but I have never been able to satisfy myself that animals upon which this latter operation had been performed recovered a physiological state sufficient to give a fair basis for comparison. Whether this be so or not, I have almost invariably found that such frogs breathe much less often than normal frogs, or those with *corpora bigemina* intact. The observations of Setschenow⁹ and others tending to demonstrate the existence in the *corpora bigemina* of a centre inhibiting the reflex actions of the spinal cord made it especially desirable to see if there were not also in them centres influencing the centre for the respiratory movements, which if not reflex in its normal working is at least largely subject to reflex control.

The general method of operating in order to remove the fore parts of the brain of the frog is too well known to need a detailed description here. After dividing the skin in the middle line, I have always removed a piece of the skull with a small trephine applied in a lozenge-shaped area which is seen to be bounded on the sides by four small vessels. The posterior edge of the opening thus made extends back to about opposite the posterior margin of the cerebral hemispheres, and the aperture was enlarged with scissors until the front edges of the optic lobes came into view. These were carefully and completely separated by a cataract knife from the parts of the brain in front of them, and the latter were removed from the cranial cavity; the incision in the skull being usually carried forwards to facilitate this removal. The edges of the skin were then brought carefully in contact, without sutures, and the animal placed in a dish containing a little water and left until the wound healed up. Usually not three drops of blood are lost, but sometimes when the operation seems to have been carried out in exactly a similar manner there

is considerable bleeding. The point most needing attention is that the optic lobes be completely severed from the parts in front of them, before the latter are pushed forwards preliminary to removal; if the optic lobes be dragged in the least the animal does not recover normally, but exhibits either for some days or permanently a tendency to lean on one side. When, on the other hand, the operation has been neatly performed, the animal from the moment that it is placed in the dish, sits up and breathes in a normal manner, exhibiting no tendency whatever to make spontaneous movements. In other cases movements may occur for some time after the operation, and if there has been much bleeding the frog squats down in an unnatural position for some hours. Sometimes too, from a cause which I have been unable to detect, the animal sits up at first in an abnormally erect position, and such rarely recover completely. My observations were made upon frogs which had assumed a normal and symmetrical position from the first, and were never commenced until at least three days had elapsed after the operation; in most cases not until after a week or more. Animals which did not exhibit lively reflex movements, and which were not capable of jumping vigorously, were not employed. The experiments were carried on upon autumn and winter frogs in the months of November, December, and January. The animals were kept in dishes containing a little water, changed daily, and in a room at from 13°-18° C.: they were not fed, as experience shewed me that for the week or two during which I desired to keep them, they did better without food: or at least without the exhausting struggle which the attempt to open their mouths called forth.

When an experiment was to be carried out, the animal was placed on the leaden platform in the manner already described and tracings taken of the throat movements at intervals of 15-20 minutes for from 1½ to 2½ hours. In this way the frog got used to its new circumstances, and a knowledge of the respiratory rhythm of the individual was obtained. The edges of the skin where they had united over the skull wound were then separated and a small crystal of pure sodium chloride placed in contact with the cut end of the optic lobes. To do this it was necessary to clear away material which had accumulated in the cranial cavity, and this usually caused some bleeding. At first I contented myself with laying the crystal of salt on the ends of the optic lobes, and left it there to dissolve in the blood which collected in the cranial cavity. In my later experiments the salt was not applied until the blood had been sopped out

by a bit of absorbent paper, and these have given more uniform results. If the "resistance" theory of the cause of the rhythm of the respiratory movements, so ably advocated by Rosenthal,⁵ and I believe now generally accepted, be employed, the immediate and most marked effect on the respiratory centre may be thus expressed: *The stimulation of the optic lobes by salt diminishes the resistance to the discharge of the inspiratory centre, usually leading for a time to a condition of tetanic inspiration, and increases the resistance to the discharge of the expiratory centre, leading to rare expirations which, when they occur, are of great violence.*

Immediately after the salt is placed upon the optic lobes the animal exhibits violent movements, which render it impossible for some minutes to get a tracing. The majority of these movements, even if the animal be placed upon a dry table, are seen to be unequivocal swimming movements, varied occasionally with movements of progression, often of the "circus" type, probably from an asymmetrical position of the salt upon the optic lobes. The animal croaks frequently and these croaks are repeated at intervals for more than an hour. The throat is held for some time in a state of retraction (except during the croaks), *i. e.* there is a tetanic inspiratory discharge and complete inhibition of the expiratory centre. In four or five minutes very powerful expirations begin to occur, the throat during the long intervals being still held retracted. In ten or fifteen minutes the animal usually becomes quiet enough to allow a tracing to be taken, although for some half an hour or longer it continues to exhibit frequent spontaneous movements; but these have no longer the swimming character; it either jumps away or crawls off the edge of the lead plate. Henceforward there is a gradual change in a uniform direction: the active expirations become more numerous and less forcible: at last, somewhat suddenly, the throat passes from a state of retraction during the respiratory pauses to one of protrusion, and for a time the respirations are more powerful than normal, less frequent, and all of the "flank" type. This gradually passes into the normal state. Three or four hours after the salt has been applied a "throat" respiration occurs now and then: these gradually become more frequent, and on the next day the animal is breathing in its usual manner, with on the average four or five "throat" respirations to one "flank," and all of about their usual force. In one or two cases the course of events has been different; after the animal had reached that condition in which the respirations are fairly numerous and all of the flank type, no further progress was made towards recovery: the respirations became feebler and rarer, at

last barely perceptible, the skin on the back dried up, and death supervened at the end of about 24 hours.

The tracing represented in Fig. 8, Plate VI [Plate 12 of this volume], is a typical one, shewing the first effect of the salt. Seven tracings taken at intervals from 11 a. m. to 12.30 p. m. had shown the animal to be breathing in a fairly normal manner, but the "flank" respirations less numerous and less marked than ordinary. At 12.35 a crystal of salt was carefully laid on the anterior cut end of the optic lobes. Croaks and swimming movements followed: then leaps and walking forwards. Respiratory movements were observed for a few seconds after the application of the salt; they then ceased entirely (except croaks) with the throat muscles in a state of retraction. At 12.43 respirations recommenced and, the animal being now sufficiently quiet, the tracing, Fig. 8, was obtained at 12.46. It shews the sudden and violent protrusions (active *expirations*) with which the throat retraction was now from time to time interrupted and the immediate return of the throat to its state of retraction (*inspiration*) after each of these expirations. Five of these respirations occurred in a minute: the average number of respirations in the seven preceding tracings was 64.5 per minute, varying from 72 to 57.5; the temperature had not altered a degree (having risen only from 16.1° C. to 16.8°). Until 1.10 this state of things remained practically the same, except that the throat protrusions became a little more numerous; but the animal was so restless as to make it impossible to get a continued trace. At 1.10 the number of respirations was 15 in a minute and they were less powerful, but the throat was still retracted in the intervals. This tracing is given in Fig. 9. At 1.22 the animal jumped out of the dish, and when replaced it was found that the periods of throat retraction had ceased: the respirations now occurred regularly at the rate of 31 per minute, were all of the "flank" type, but more powerful than normal: see tracing, Fig. 10. This condition lasted for some time; then one or two "throat" respirations per minute occurred, and at 3.35 "throat" and "flank" respirations alternated nearly regularly, and the throat protrusions of the "flank" respirations had diminished to about their usual size (Fig. 11).

This example, selected from a number which essentially agree with it, shews clearly enough the influence of stimulation of the optic lobes upon the resistances to discharge of the inspiratory and expiratory centres, but a close examination shews that this is not the whole effect: *the amount of discharge in a given time is also influenced, being diminished*

for the inspiratory and increased for the expiratory centre. Adopting the usual theory, this might be brought about either by an influence exerted upon the irritability of those centres, or by an alteration in the amount of stimulus acting upon them in a given time, or by both these together; of these three possible methods the first seems to me the most probable, as it is difficult to conceive how the stimulation of the optic lobes could affect the total amount of stimuli acting upon the respiratory centres. Adopting it provisionally, the above fact might be expressed by the statement that *irritation of the optic lobes diminishes the irritability of the inspiratory centre and increases that of the expiratory.* In Fig. 8 this effect is not very easily recognised, especially as regards the inspiratory centre, for it is almost impossible to form an opinion as to how much discharge in a unit of time is represented by the continued throat retraction periods. It is more obvious as regards the expiratory centre, for while the expiratory discharges are only between two and three times less numerous (5 to 12 or 15) in a minute than normal, they are certainly far more than three times as powerful. In the tracing given in Fig. 9 this is still more obvious, for while the expirations have now about their normal rate (15 per minute), they are considerably more powerful. In Fig. 10, when the throat retraction periods have ceased, we see clearly the less than normal amount of discharge from the inspiratory centre. The resistance to the discharges from this centre is still small, though now beginning to increase as the influence of the salt passes off, but nevertheless the discharges are less frequent than normal, and appear only to be called forth by that compression of the lungs by the expiratory muscles which I have already referred to as the probable cause of the greater throat retractions of the "flank respirations." If the amount of discharge were not less than with unirritated optic lobes, we should certainly, with the small resistance now present, have a "throat respiration" at the points marked *a* in tracing 10, where the horizontal line drawn by the lever indicates that the throat was for some time at rest in its position of equilibrium before the next expiration (a "flank" one), indicated by the sudden descent of the curve, occurred. In Fig. 11 too, where the throat respirations have recommenced, their small number (in spite of the slight resistance to the discharges of the inspiratory centre, indicated by their feebleness) shews that the amount of discharge from the inspiratory centre in a given time is less than normal.

This general fact, of the diminution of the amount of discharge in the unit of time from the inspiratory, and its increase from the expira-

tory centre, is however much more readily recognised in some other cases, of which I will give one in detail (see next page), as it also shews the influence of feeble stimulation of the optic lobes, which illustrates the same fact. The time in this case, as in all the others, was taken for each tracing separately by an ordinary magneto-electric chronograph worked by a metronome; and the number of respirations per minute given in columns 4 and 5 was always counted for a full minute unless the frog moved away sooner, or some accident made part of the tracing illegible. In these latter cases the fraction of a minute during which the respirations were actually counted is indicated in column 4 by the numbers in brackets.

This experiment again shows quite clearly the influence of powerful stimulation of the optic lobes in diminishing the resistance to inspiratory, and increasing that to expiratory, discharges. The salt first produced tetanic throat retraction, with total inhibition of the expiratory centre. Then (Obs. 19 and 20) a state of things like that represented for another frog in Fig. 8 (the animal being in this case too restless to allow the corresponding tracings to be taken), viz. long periods of tetanic throat retraction interrupted by rare and violent expirations, after each of which the throat retraction was immediately resumed. This opposite effect upon the two centres is however most clearly shown in Observations 21-31 (Figs. 15, 16, 17), where the feeble inspiratory discharges (except when increased in the manner before pointed out, by an immediately preceding expiration) contrast strongly with the powerful expirations, whose force shews that the impulses originating in the expiratory centre had to gather great head before they could overcome the resistance to their discharge. Inversely of course the feeble extent of the unaided inspiratory movements shews that the resistance opposed to inspiratory discharges was abnormally small.

EXPERIMENT. DECEMBER 17, 1877.

Frog, a not full grown *Rana lentiginosus*, about size of *R. temporaria*. Central hemispheres and optic thalami removed on Dec. 11. Animal did well from the first. Kept in a room at temperature of from 12°-16° C. Put in experimental trough at 10.45 a. m., Dec. 17th.

Number of Observation.	Time.	Temperature C.	Total Respirations per Minute.	Flank Respirations per Minute.	Remarks.
1	A. M. 11.0	13.7°	45.5($\frac{2}{3}$)	12.5	Part of this tracing is given in Fig. 4.
2	11.15	13.9	45.0	8	
3	11.30	13.9	44.0	3	
4	12.0	14.1	43.0	None in the minute counted.	
5	P. M. 12.15	14.2	45.0	"	Cranial cavity opened by pushing apart the edges of the skin where they had united. Anterior part of cranial cavity sopped out with a cone of filter paper, and the anterior cut ends of the optic lobes were seen, covered by a translucent layer of "organising lymph." The latter was not removed, but an extremely small crystal of sodic chloride was laid upon it. The animal became restless for a few minutes; walked about; jumped once or twice; made no swimming movements; did not croak. No permanent throat retraction such as always follows powerful stimulation with salt. Fig. 12. Here was obviously an increase to the expiratory discharge in a given time. The flank respirations are as powerful as when they occurred previously (Fig. 4), and considerably more numerous. How much of this was due to the salt is, however, problematical. Tracing essentially like that in Fig. 12.
6	12.30	14.8	45.0	"	
7	12.42	14.9	53.0	17.5	
8	12.50	14.9	51.0($\frac{1}{3}$)	16.0	
9	12.58	15.1	55.5	5.0	
10	1.5	15.1	53.0($\frac{2}{3}$)	8.5	
11	1.15	15.2	51.0($\frac{2}{3}$)	8.5	
12	1.25	15.2	50.5	3.75	
	1.30				

Fig. 13. Tracing now of normal type for this frog, which as preliminary tracings (Obs. 1-6) shew, was characterised by the small number of its active expirations. The layer of material on the cut ends of the optic lobes was removed carefully, and a small crystal of sodic chloride placed directly on

Number of Observation.	Time.	Temperature C.	Total Respirations per Minute.	Flank Respirations per Minute.	Remarks.
	P. M.				
13	1.35	15.2°	55.5	55.5	their cut surface. Respiration ceased entirely for a short time. Animal performed circus movements; no swimming movements or croaking. Retraction of throat passed off in a minute and the respiratory movements recommenced; but each was now seen to be of the "flank" type, <i>i. e.</i> , accompanied by a discharge from the expiratory centre. The brief throat retraction was no more than might be produced by simply handling the animal.
14	1.40	15.2	50.0	48	Fig. 14. In the tracing it is not obvious that all the respirations were "flank," but the fact was established by direct observation of flanks and nares. Here there seems to be an obvious influence of the salt increasing the discharge from the expiratory centre in the unit of time; for the resistance (indicated by the extent of each movement) is about normal as seen by comparison with flank respirations of Fig. 4 taken from the same animal, while the number of expiratory discharges per minute is greatly increased. The state is comparable with that represented in Figs. 10 and 19, where the influence of a more powerful stimulation is beginning to pass off.
15	1.45	15.2	50.0	36	
16	1.50	15.2	48.0	37	
17	2.0	15.6	50.0	30	
18	2.20 2.22	15.7	50.0	27	
19	2.38	15.7	About 16	About 16	As the effect of the salt was now obviously passing off a somewhat larger crystal was placed in contact with the cut ends of the optic lobes. The animal croaked; clonic spasms set in and lasted for a few seconds; then swimming movements. Throat powerfully retracted and no respiratory movements seen until 2.33, when one occurred; the next at 2.35, followed by several croaks. Animal remained restless for some time, so that no tracing could be obtained. An attempt made to obtain a tracing was frustrated by the restlessness of the animal. The one or two curves that were obtained showed that it was breathing as the frog represented in Fig. 8, that is with long throat retraction pauses, and powerful expiratory discharges at intervals.
20	2.45	15.8	About 8	About 8	Animal too restless to allow a satisfactory trace to be taken. Character of respiratory movements same as in Obs. 19.

Number of Observation.	Time.	Temperature C.	Total Respirations per Minute.	Flank Respirations per Minute.	Remarks.
21	P. M. 3.0	16.0°	62	6	<p>Fig. 15. Here we find some resistance to the inspiratory centre beginning to arise. The throat retraction is no longer tetanic, but while still, on the whole, retracted. The throat has very feeble rhythmic movements of return towards its position of equilibrium, but the resistance permitting these rhythmic relaxations is so feeble that it is overcome almost at once, long before the throat has returned to that position; thus very feeble throat respirations are produced. With reference to the expiratory discharge, the rise of the curve at <i>a</i> is not due to a respiratory movement proper, but to the fixing of all the muscles of its body by the animal before making the violent expiratory effort. By this fixation it sits up rigidly and more erect, and the lever, following the throat as it rises with the rest of the head, produces the curve ascent at <i>a</i>. Similarly the descent at <i>b</i> is not due to a throat movement proper, but to a sudden relaxation of its muscles and collapse of the whole animal after its violent respiratory effort. This fixation of all the muscles of the body before the violent expiratory discharge is very common in frogs in the most powerful stage of optic lobe irritation.</p> <p>The "throat" respiratory curves too feeble to be counted with certainty. If there be any error the number is too large.</p> <p>Ditto.</p> <p>Ditto.</p> <p>Traces essentially like Fig. 15.</p> <p>Fig. 16. "Throat respirations" now well marked, though still very feeble. Rise of curve at <i>a</i> produced in same way as similar rise in Fig. 15. The irregularity in the ascent after the expiration is of course due to imperfect action of the writing point.</p> <p>Fig. 17. Compare with Fig. 9, from which it differs in the fact that it presents small rhythmic movements during the throat retraction periods, the inspiratory discharge not being here quite tetanic. The breaks seen in the ascending limb of the larger curves in each figure depend probably on the fact that the first part of the ascent represents the passive return of the hyoid to its position of rest; the part above the break is due to contraction of hyoid elevating (inspiratory) muscles.</p> <p>A return to the type of respiration seen in Obs. 21-27. (Figs. 15 and 16).</p>
22	3.5	16.0	45.0 (?)	3	
23	3.15	16.1	49.0 (?)	4	
24	3 (?)	16.1	49.0 (?)	4	
25	3.35	16.0	48.0	3	
26	3.45	16.0	52.0	3	
27	4.5	16.1	59.0	3	
28	4.30	16.1	47.0	12	
29	5.0	16.2	47.0	2	

Number of Observation.	Time.	Temperature C.	Total Respirations per Minute.	Flank Respirations per Minute.	Remarks.
30	P. M.	16.2°	49.0	2	Animal pushed away the lever and crawled out of the dish soon after the tracing of Obs. 31 was taken. When it was replaced and things were made ready for the next tracing it was found that the stage characterised by the long respiratory pauses with throat retraction had passed off.
31	5.5 5.30	16.4	43.0	4	
32	6.0	16.8	37	15	Fig. 18. Respiration now fairly normal, except that the "flank" respirations were more numerous.
33	6.10	16.8	36	32.5	Fig. 19. Almost exactly like Fig. 10. Abnormally powerful and frequent "flank respirations," with rare (3.5 per 1') throat respirations. This stage almost invariably precedes such a stage as that represented in Fig. 18, and gradually passes into it, the "flank respirations" becoming less powerful and less frequent, and the "throat respirations" more frequent until the normal respiratory modus is resumed. The skipping of this stage for a time in this case (as shown in Fig. 18) is, therefore, probably to be ascribed to the sensory stimuli applied to the animal, in replacing it in the dish, readjusting the lever, etc.
34	6.30	17.1	37	34	Animal having now reached the stage which I knew from previous experiments would pass with extreme slowness into the normal condition, the observation was discontinued until the next day.
35	Dec. 18 12.30 P. M.	16.4	52	18	Fig. 20. Compare with Fig. 4 from same frog before the salt was applied. On Dec. 19 several tracings were again taken from the frog; these were quite normal, but the active expirations more numerous than they were on Dec. 17 before the salt was applied. The difference was, however, not greater than may be seen on different days in frogs on which no experiment has been performed.

Turning now from the resistance opposing an individual discharge, to the total amount of inspiratory or expiratory discharge taking place in a given time, we find in the tracings, I think, evidence of the proposition stated above, that the total inspiratory discharge, in say a minute, is diminished and the expiratory increased. Taking the expiratory centre first, we find that in this frog before the salt was applied it was hardly active. In Obs. 4, 5 and 6 it did not discharge once a minute, yet the resistance to it was not great, as shewn by the only normally large discharge when it did occur. When the optic lobes were very feebly stimulated active expirations became much more numerous (Obs. 7-12), the resistance still remaining practically unaltered; but it may be doubted whether this increase was not due rather to the general irritation of the frog in holding it to open the cranial cavity, etc., than to the immediate influence of the small salt crystal, acting through the layer of material covering the ends of the optic lobes. When however this layer was removed, and a very small salt crystal carefully applied directly to the optic lobes, a much more definite result was obtained: there were 55.5 expiratory discharges in a minute (Obs. 13), each of about its usual amount, so that the resistance did not seem to have been affected by this amount of stimulation; the slightness of which was further evidenced by its not calling forth croaks or swimming movements. The state of things is in fact very like that seen later when the influence of more powerful stimulation was beginning to pass off. When more salt is applied so as to affect also the resistance to the discharge of the centre it is much more difficult to make an estimate of the amount of discharge in a given time, since it is hard to get even an approximate idea to how many of the smaller discharges one of the larger is equivalent. When the effect of the salt begins to pass off however, and the resistance to the expiratory discharges becomes again somewhat less, it becomes also easy to see that the total expiratory discharge in a given time is above the normal. In Observations 33 and 34, *e. g.*, there are more than thirty expiratory discharges in a minute, and each of more than normal amount.

With reference to the inspiratory centre, the influence of the stimulation of the optic lobes upon its total discharge in the unit of time is also difficult to estimate in the stage of greatest stimulation; the throat is then tetanically contracted, and one cannot say to how many normal discharges a given period of this retraction is equivalent. But when this condition begins to pass off and feeble throat movements appear, it seems tolerably plain that they represent less than the normal amount of

discharge from the inspiratory centre. In Obs. 21 (Fig. 15), where the total number of respirations is 62 per minute, it might be supposed perhaps that in spite of the feeble resistance overcome, as indicated by their small extent, the increased number (as compared with the average number of inspirations, 45 per minute, before the salt was applied) made up for the deficiency in size. But in Observations 22-28 it is seen that the average number of inspirations per minute is under fifty, and here the increase in number of 3 or 4 per minute certainly does not compensate for the diminution in amount of each. Were the resistance as small as these feeble movements shew it to be, and at the same time the total discharge from the inspiratory centre anything approaching its normal amount (see Fig. 4), the number of inspiratory discharges per minute would certainly rise far above 50.

So far then as stimulation of the optic lobes is concerned, we have, I think, sufficient evidence to justify the propositions which I stated, before giving the experimental details upon which they were based. It would have been, no doubt, desirable to observe if, when the full effects of optic lobe stimulation had manifested themselves, the severance of those parts from the medulla removed those effects. But as Kramszük⁸ has pointed out, a frog whose brain in front of the medulla is removed, will not stay still a moment; it crawls about for hours, presenting a striking contrast to the motionless frog with its optic lobes. It is therefore impossible to get a respiratory tracing from such frogs, at any rate in their normal position, until some hours after the operation has been performed, when it would be useless for comparison; and then, moreover, as I pointed out above, the animals seem thoroughly exhausted and in an unphysiological state.

In the facts, however, that the characteristic results of the stimulation were not called forth, at least to nearly their full extent, unless the salt was so applied as to excite centres (those for croaking and swimming) known to be situated in the optic lobes, and that when these centres were excited the characteristic effects on the respiratory movements never failed to appear, we have, I think, strong presumptive evidence that these effects depend on stimulation of an optic lobe centre. That they do not depend upon the salt soaking through and attacking the respiratory centres in the medulla directly, seems to be shewn by the rapidity with which the application of the salt to the optic lobes is followed by the respiratory disturbance; within a few seconds tetanic throat retraction is usually seen. That they do not depend merely on the stimulation of the

cut ends of fibres which passed from the fore brain through the optic lobes to the medulla oblongata, but on the stimulation of an optic lobe centre, seems to be shown by the fact that when the amount of salt applied is so small as not to excite other optic lobe centres (Obs. 13 in the experiment given in detail), the characteristic respiratory effects are also in great part wanting. The salt appears to be required in sufficient quantity to penetrate into the optic lobes, mere stimulation of the cut surface not being sufficient, as it would be if the effect were due to irritation of fibres passing as above supposed.

Another objection may be raised to the view which I have taken, an objection based on the long continuance of the effect of the stimulation; which may be supposed to indicate rather the paralysis, due to injury, than the excitement of a respiration-regulating centre in this part of the brain. The reasons which lead me to ascribe the effects to a stimulation rather than a paralysis are these. First, the complete recovery of the animal in most cases; this shews that there has been at least no actual destruction of the regulating centre, such as might be supposed to be brought about by the action of the salt. Second, the action on the other centres of the optic lobes is obviously excitant; the croaking, swimming, and locomotor centres are all stirred up to activity, and it is *a priori* improbable that the same influence which excites them will paralyse the respiration-regulating centre. Third, the activity aroused in some other optic lobe centres by the salt lasts nearly as long as the effects on the respirations. The swimming movements soon cease; but the animal has a tendency to crawl about for nearly an hour in many cases, not continuously it is true, but at short intervals; so that we have a tolerably long-lasting irritation of the centre exciting and coordinating the locomotor apparatus. The croaks, too, occur at intervals in many cases for more than an hour and a half; but the centre whose excitement lasts longest is that inhibiting the reflex actions of the cord (Setschenow⁹). Again and again I find in my notes that the time when the animal begins once more to show reflex irritability is just when the influence of the salt upon the respiratory movements is beginning to pass off, or after it has commenced already to weaken. I find it nearly always noted that the animal, after having borne the lever without trouble or readjustment for a considerable time (commencing from the cessation of the crawling movements), "now begins again to shew signs of reflex irritability," pushing the lever away, or sometimes crawling off the edge of the dish, such reflexes having been suppressed hitherto from the time of applica-

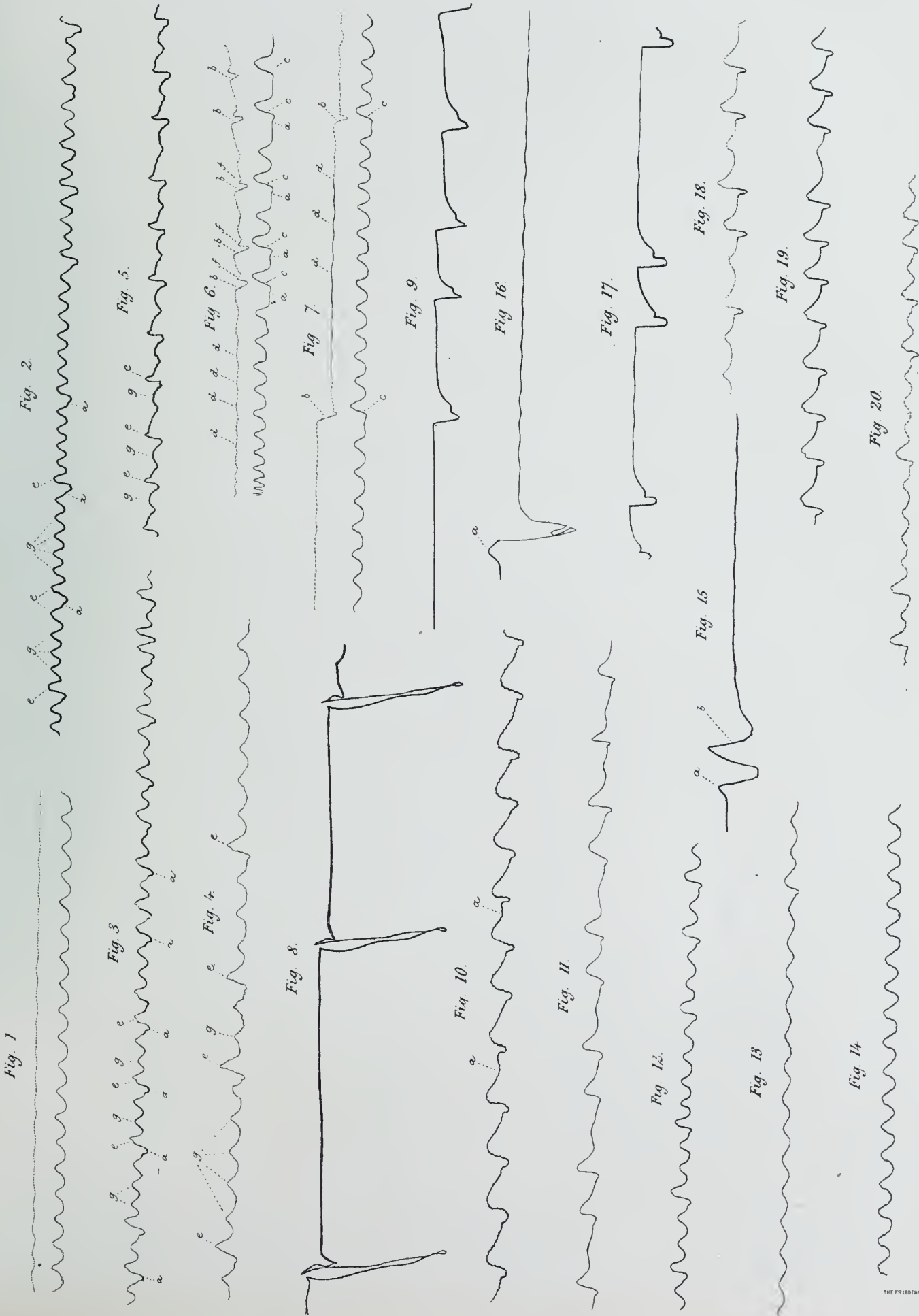
tion of the salt. In the experiment given in detail, *e. g.*, the frog gave no trouble from 2.45 p. m., when (in this particular case) the crawling movements had ceased, until after 5.30 p. m., when it pushed away the lever and crawled out of the dish, shewing that the excitement of the inhibitory centres of Setschenow had lasted until that time; and immediately after this, as the next tracings shew, the frog began its steady progress back to a normal mode of breathing. The long continuance of the respiration-modifying effects of the salt applied to the optic lobes is then not by any means inconsistent with the view, more probable on other grounds, that its action is stimulant rather than paralysing. On the other hand, the almost invariable connection which I have found between the time when the inhibitory effect of optic lobe stimulation on the general reflex actions of the animal begins to pass off and the time when the respiratory effects begin also to pass off, suggests strongly a close relationship between this respiration-regulating centre and the general reflex-regulating centre, even should the two not be identical. Two experiments with injection of quinine into the dorsal lymph sac, made with the view of seeing whether the quinine excited the respiration-regulating centre, as it has been stated to excite the reflex-inhibiting, gave me no definite results; but the animals were not in a satisfactory state, my winter supply of frogs having run short.

Several theoretical points of interest are suggested by the results of the foregoing experiments, but most require further investigation, and I will only refer to one here. The rhythmic alternation of the innervation of expiratory and inspiratory muscles may be accounted for, either by supposing the existence of independent, though closely related, inspiratory and expiratory nervous centres (Budge), or by the hypothesis of a single respiratory centre capable of discharging to either group of muscles according to circumstances. Rosenthal⁵ discusses the question and decides in favor of a single centre, with two resistances in relation with it; one intercalated on the road to the inspiratory nerves, and the other on that to the expiratory. Whether an inspiratory or expiratory discharge shall issue from the centre will then depend on the ratios of the two resistances; and since in most mammals the expiratory resistance is greater, no active expirations occur at all in their normal breathing. The results of optic lobe stimulations shew that this hypothesis will not hold good for the frog, since they make it obvious that impulses tending to produce expiratory discharges have not the path to the inspiratory muscles open to them. For, during stimulation

of the optic lobes, the resistance on the latter route is abnormally small, as shewn at first by the tetanic contraction of the inspiratory muscles, and later by the feeble throat respirations, while the resistance on the expiratory route is abnormally large. If the impulses originated in the same centre and took merely the more open road, there could arise no such accumulation as that which finally overcomes the enormous resistance to the expiratory discharges and calls forth the powerful expiratory movements depicted in Figures 8, 15, 16, etc. We must assume that the impulses which finally break forth along the expiratory nerves are not able to travel into the inspiratory nerves; and that we have really two distinct centres, one for inspiration and one (normally less easily discharging) for expiration, and that each has its own stimulus and generates its own nervous impulse which can travel only to its own set of muscles, quite independently of the resistance opposed to discharge from the other centre.

This seems also a necessary deduction from the normal mode of breathing in the frog, for were both inspiratory and expiratory muscles innervated from the same centre no "flank respirations" could occur, the resistance along the paths to the muscles producing the throat respirations being less than that in the paths to the expiratory muscles of the flanks: the nervous impulses would, so to speak, be constantly "tapped" and never accumulate so as to discharge to the flank muscles. As these latter, however, do contract at intervals, this tapping clearly does not take place with respect to the impulses generated for the expiratory muscles, which finally gain head (the throat movements not renovating the air in the lungs as the inspiratory discharges with passive expirations do in the lungs of the mammal) until they overcome the opposing resistance. In what manner the immediately succeeding greater inspiratory discharge is brought about, I have already tried to explain.

In conclusion, I would point out that the results of chemical stimulation of the optic lobes in the frog seem to agree very well with the results of electrical stimulation of the corpora quadrigemina in the mammal, as described by Ferrier.⁷ His account, it is true, is somewhat indefinite, and is given as a confirmation of results of Danilewsky's, which the latter did not obtain. Ferrier's words, speaking of the effect of stimulation of the interior of the corpora quadrigemina, are "the respiratory rhythm is also altered in a marked degree; irritation causing a deep inspiration, followed by prolonged and powerful expiratory efforts." Here it seems probable that between the expirations the chest was in a



tetanic inspiratory position; and if so, the state of things will almost exactly correspond with the results of chemical stimulation of corresponding parts in the frog.

NOTE. The very small secondary curves seen in some of the tracings in Figs. 4, 10, 20, etc., are due to vibrations of the stand carrying the lever, the floor of my work-room being unfortunately not very steady.

BALTIMORE, *March* 18, 1878.

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XI.

THE INFLUENCE OF STIMULATION OF THE MID-BRAIN UPON THE RESPIRATORY RHYTHM OF THE MAMMAL.

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With Plate 13.

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One of us having found (*Journ. of Physiol.*, Vol. I, p. 131) that chemical stimulation of the midbrain of the frog causes an alteration in its mode of breathing characterised by accelerated or tetanic inspiratory and impeded expiratory movements, the following experiments were undertaken with the object of ascertaining if the same phenomena were exhibited by the mammal. In the paper above referred to (p. 170) a bibliography is given of observations previously made as to the effects of cerebral stimulation upon respiratory movements; we have seen nothing since which calls for addition to that list.

Our first attempts at recording the rate and extent of the respiratory movements were made either by means of a flat inflated sac, connected with a recording tambour, introduced between the liver and the diaphragm through an incision in the *linea alba*; or by direct observation of the diaphragm exposed from the abdominal side. Neither of these methods was satisfactory, and we therefore had recourse to the following. Tracheotomy having been performed, a glass T-piece was tied in the windpipe: one limb of the T-piece had attached to it a short piece of india-rubber tubing: from the other limb a tube led, through a hole in the cork, into a large glass jar: through the cork of this jar passed another tube which was connected with a Marey's recording tambour, the lever of which wrote on a revolving cylinder. Near the bottom of the jar was an aperture which could be opened at pleasure, so as to set its cavity in communication with the surrounding air in the intervals of the observations. In these intervals the short india-rubber tube above mentioned was left open, and served for the animal to breathe through: when an observation was to be made this tube was closed by pressing between the thumb and finger or by a screw clamp, and the animal then breathed

into and out of the glass jar: the variations of pressure produced in the latter were recorded by the tambour, *which was inverted*. Consequently, when the animal's chest expanded (*i. e.* during inspiration), air passed into it from the jar and tambour, and the lever of the tambour ascended; the reverse of course occurred during expiration. By this means we found that very small respiratory changes in the capacity of the chest were very distinctly recorded while, as we satisfied ourselves by several experiments, the size of the jar was such that no dyspnoea of importance was caused by the animal's being compelled to respire from it for at least a minute. Fig. 1, Plate XIV [Plate 13 of this volume], shews a tracing, taken without any stimulation, for more than 90 seconds. An explanation of it will serve to elucidate the other figures also. The small movements at *a* are those traced by the tambour lever before the closure of the short india-rubber tube on one limb of the T-piece. On screwing up the clamp closing this, the respiratory tracings increase in extent and rapidly attain a maximum, which is then maintained nearly constant, both as regards their amplitude and rate, until *b*, when the short tube was opened again: there is no sign whatever of that tetanic fusion of the respirations which, as will be seen subsequently, follows the midbrain stimulation. The line *x* is the base line traced by the tambour lever after we had disconnected the glass jar from the trachea and placed it in communication with the exterior air, while the drum made a second revolution. The line *s* was traced by the stimulation lever, to be hereafter mentioned. The time is indicated on the line *t*, traced by an electric chronograph in connection with a seconds clock. In the respiratory tracing there is a slight indication of a phenomenon, which in two or three cases occurred to a large extent and rendered the experiment useless, *viz.*, a larger absorption of gas by the lungs than was compensated for by exhalation, so that the total volume of gas in the apparatus was diminished, and the lever-tracing left the base line entirely. In the great majority of cases, however, this is entirely absent, or occurs to a very slight amount.

Rabbits were the animals employed throughout, except a couple of confirmatory observations on cats. After the insertion of the tube in the trachea, the general course of the experiment was as follows. The animal, still under ether, was turned over and the skull opened over the midbrain. The transverse sinus, which lies over the posterior tubercula quadrigemina, was thus exposed. If the posterior tubercula were those which it was desired to stimulate, a pair of needle electrodes, covered

with a thin layer of sealing wax, except for $\frac{1}{8}$ inch at the tip, were inserted; this we were generally able to do without penetrating the sinus: when the latter was pricked we usually succeeded in stopping the bleeding by tying the sinus carefully on each side of the wound. The electrodes were borne by a wire framework attached to the head holder of Czermak's rabbit bed, and so followed the movements of the head of the animal if it jerked it; in this way any tearing of the brain, which at first gave us much trouble, was avoided. If, on the other hand, it was desired to insert the electrodes into the anterior tubercula quadrigemina, either the posterior parts of the cerebral hemispheres were first removed, or, more frequently, the whole of them, as we found the latter operation, as a rule, caused less bleeding.

The electrodes were connected with the secondary coil of a du Bois induction apparatus, with magnetic interruptor; the current from a single carbon-bichromate cell was sent through the primary coil. In the secondary circuit was interposed the stimulation lever above referred to, which marked on the drum in the usual manner, when the current was sent through the electrodes. With reference to this marking, one point may require notice. At the commencement of an observation all three levers, time, stimulation, and respiratory, were placed in contact with the drum and on the same vertical line, the respiration lever being in that position (base line) which it assumed when the jar, with which the tambour was connected, was disconnected from the trachea, and in free communication with the external air. When the jar was closed and connected with the trachea, the respiration lever described large curves, and was no longer on the same vertical line as the other levers, except at the moments when its tracing cut the base line. Consequently, to find at any moment what part of the stimulation line corresponds to a given part of the respiratory tracing, it is necessary to draw a perpendicular from the stimulation line at that point to the base line, and from the point where it meets the latter to draw a line parallel to the curves of the respiratory tracing until it meets the latter: this point of meeting will be the point in the respiratory curve answering in time to the given point in the stimulation line. The same is of course true for the relationships of the time and respiratory tracings. In Fig. 6, *e. g.*, where the stimulation has lasted for 9 seconds (from s' to s'), the point of the respiratory trace which answers to the moment of cessation of the stimulus is not that at which the perpendicular px' cuts the respiratory tracing; but is to be found by drawing from x' the dotted line $x'z$ until it cuts the respiratory

tracing. The point of the respiratory trace, which answers in time to the commencement of the stimulation, is of course to be found similarly. These dotted curves have not been drawn for the other figures in most cases, but the same reasoning applies to all.

After the completion of the operation the animal was left for some time, usually an hour, to recover from the shock of the operation. The midbrain was then stimulated during a minute and a half, in the manner above described, generally for periods of 10-12 seconds at a time, with intervals of 10 seconds rest. An interval of 10-15 minutes was then allowed to elapse, and the stimulation repeated with varying positions of the secondary coil. During the stimulation the etherisation was not pushed to the most complete narcosis, as otherwise inconveniently strong currents were required to produce any effect.

The general result of our experiments may be summed up thus: *There lies deep in the midbrain of the rabbit, beneath the posterior corpora quadrigemina and close to the iter, a respiration-regulating centre, similar to that in the corpora bigemina of the frog: electrical stimulation of this centre causes accelerated inspirations finally passing into tetanic fixation of the chest in an inspiratory condition: and correspondingly diminishes or altogether inhibits expiration.* If the animal be young and the operation have been performed without loss of blood, these results follow extremely feeble stimulation: stimulation, for example, with the secondary coil at 20 or 22, so feeble as to be barely perceptible when the electrodes are applied to the tongue.

Figures 2, 3, and 4 give the results of one experiment (Rabbit, April 25, 1878). The posterior part of the cerebrum was exposed at 11 A. M. with hardly any loss of blood: the electrodes were inserted at 12.15 P. M., and as ascertained by *post-mortem* examination, the right electrode rather superficially in the right posterior corpus quadrigeminum and the left deep in the corresponding body on the left side. Fig. 2 gives the effects of four stimulations at 12.20. In the figure the lines *tt*, *ss*, and *x* are as in Fig. 1. The numbers beneath the stimulations give the position of the secondary coil during each. It will be seen that with the secondary coil at 20 the chest passed into a marked inspiratory condition, and never returned to its normal expiratory state during the stimulation. The inspiration is not, however, tetanic, but there are feeble attempts to return to the expiratory state, interrupted almost immediately by a fresh inspiration; we have in fact a number of very feeble rapid inspirations, which have the effect on the whole of keeping the chest fixed in an inspi-

ratory condition. With the secondary coil at 22 this effect is still well marked; at 24 much less so, and at 25 it is only just recognisable. Fig. 3 shews the results of three stimulations at 12.30, with the secondary coil at 19, 18 and 17 respectively; the tracings are of the same character as in Figure 2, but the influence of the stimulation is even more marked, especially that with the secondary coil at 17. Fig. 4 gives the results of stimulations commencing at 12.45, with the secondary coil at 16, 15 and 14 respectively: the last it will be seen passes into a continued inspiratory tetanus. Between each of these latter three stimulations a pause of two minutes was allowed, during which the animal was permitted to breathe freely. An attempt to get a more marked inspiratory tetanus by stronger stimulation failed (Fig. 5), the chest becoming relaxed during the stimulation: to this phenomenon we will return presently.

Figure 6 (Rabbit, March 29, 1878) shews a more perfect inspiratory tetanus, which is interesting from the resemblance of some of its features to those of an ordinary muscle tetanus; as for instance in the stimulation being at first insufficient to cause complete fusion of the discharges, but afterwards becoming so, as is the case in a muscle when fatigue comes on. On the other hand, in the mode of disappearance of the tetanic effect on the cessation of the stimulus, at first slowly and then more rapidly, we have a marked difference from a muscular tetanus. In this case the secondary coil was at 10.

We have numerous tracings resembling those just described, but it would be wearisome to give them in detail as they offer no essential points of difference. The reasons which cause us to locate the respiration-regulating centre in the precise locality above mentioned are as follows. When both electrodes are placed superficially in the corpora quadrigemina no respiratory effects follow even with tolerably strong currents. On the other hand, when either one or both are pushed down to the level of the *iter* the results always follow (except when there has been much bleeding or when the animal is deeply narcotised), whether they be in the anterior or posterior tubercula; but the results are purer and obtained with weakest currents when the electrodes are in the posterior. When well placed in the latter very marked and characteristic effects can be obtained with extremely feeble currents, and they are then unaccompanied by any other disturbances. If the current is a little stronger general slight tremor of the whole body accompanies the respiratory effects. This tremor, which is so common an expression of terror, is interesting in connection with Ferrier's view that the midbrain mainly

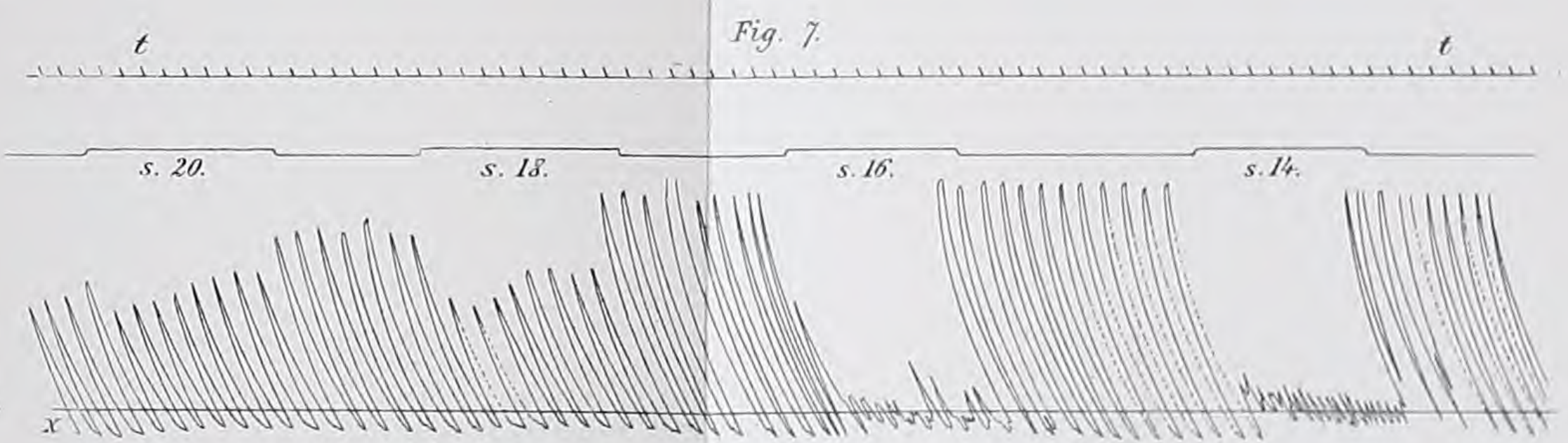
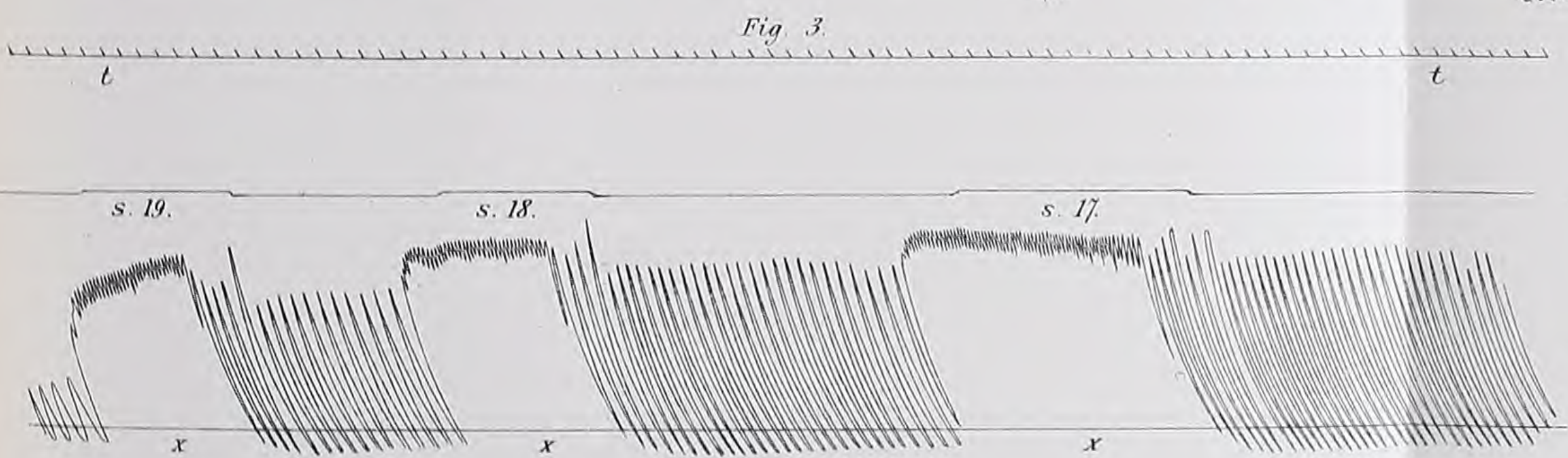
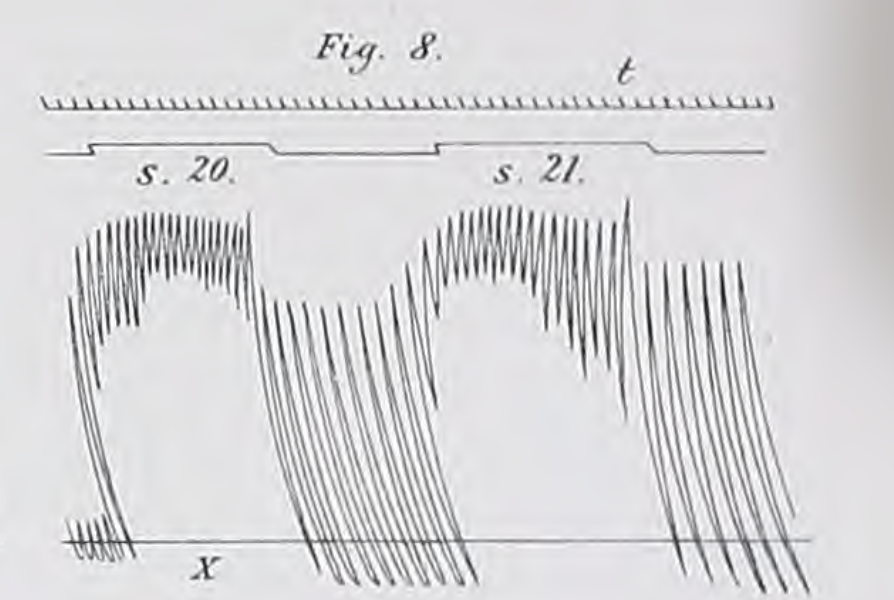
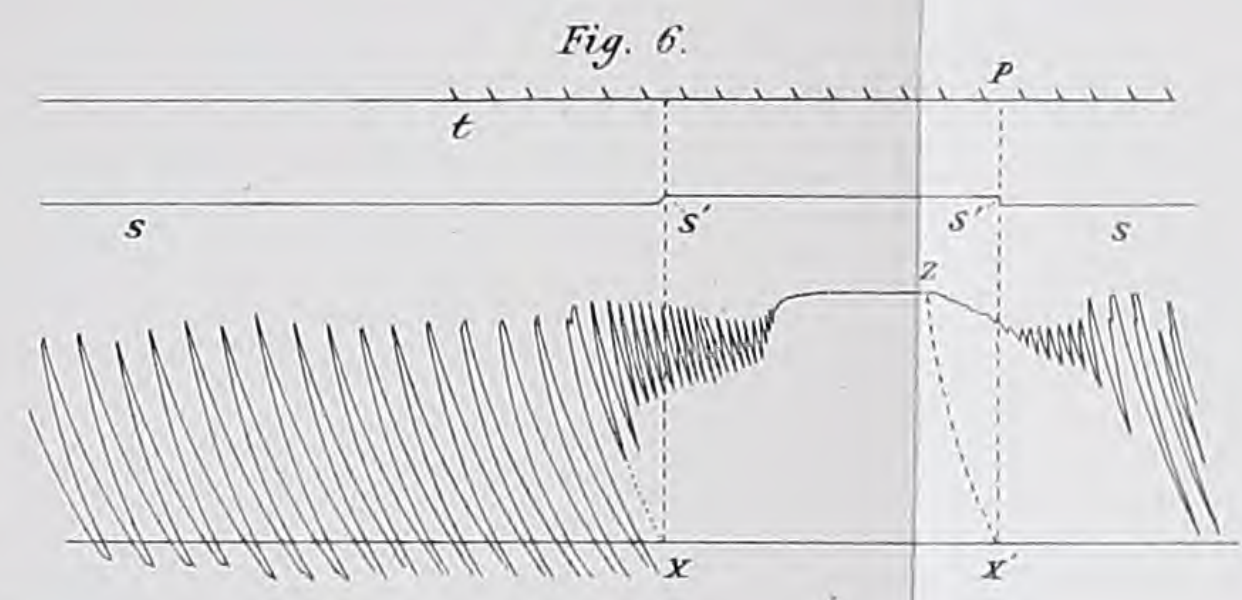
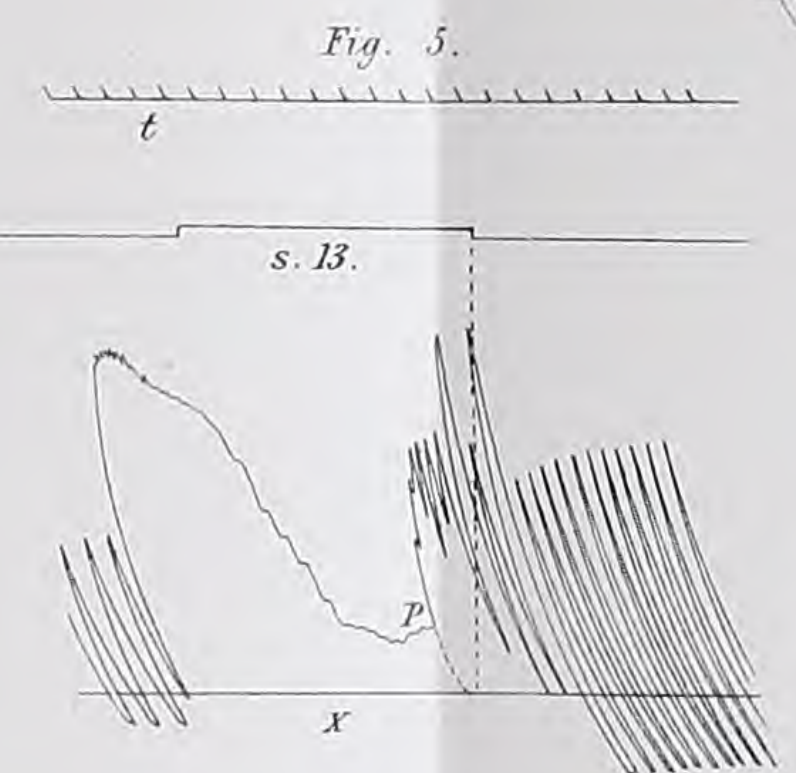
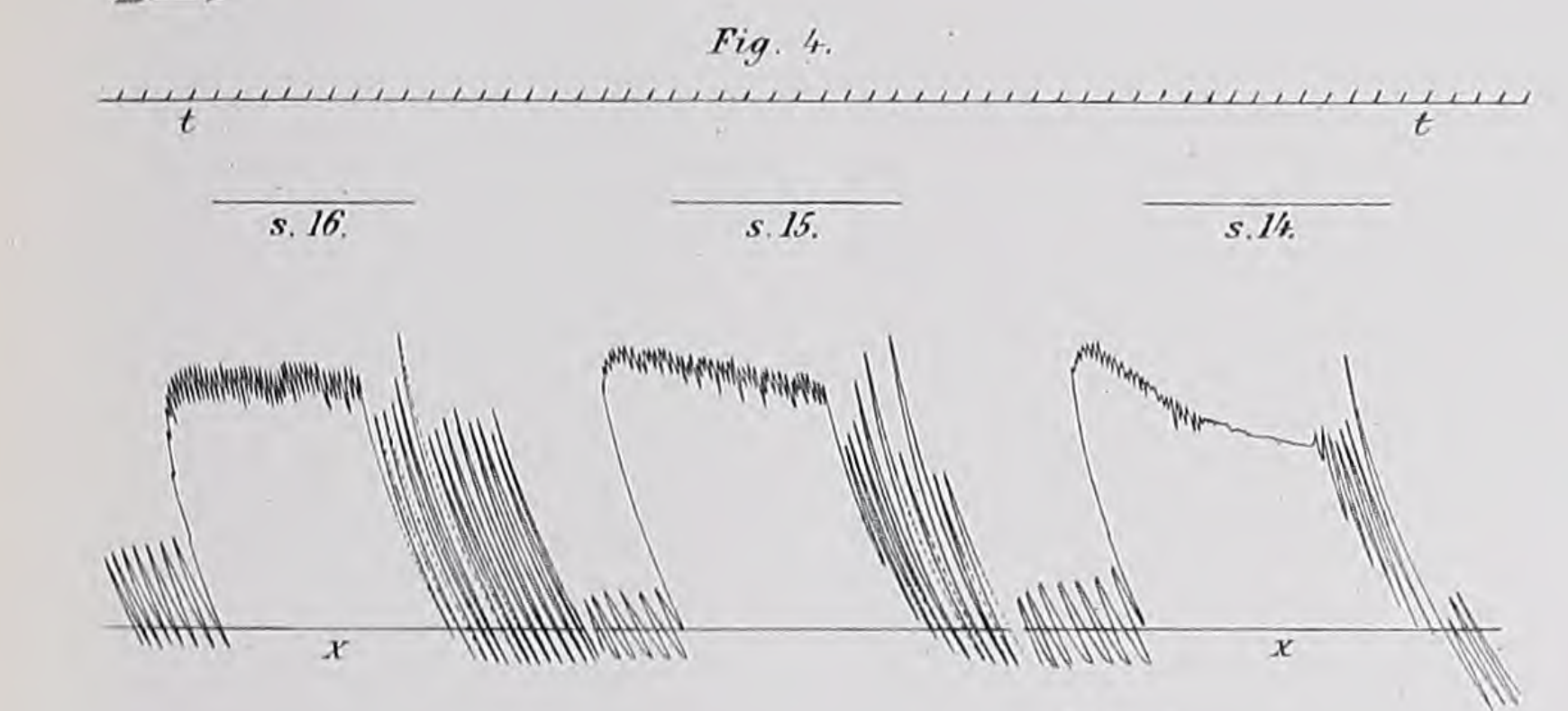
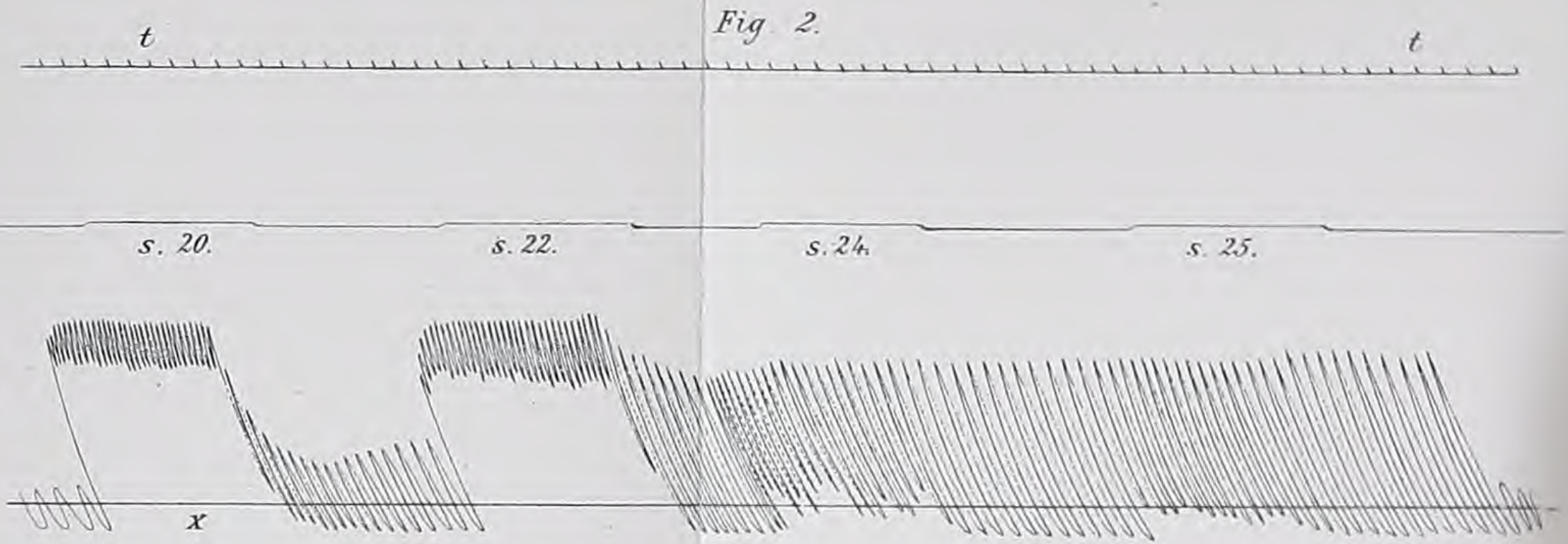
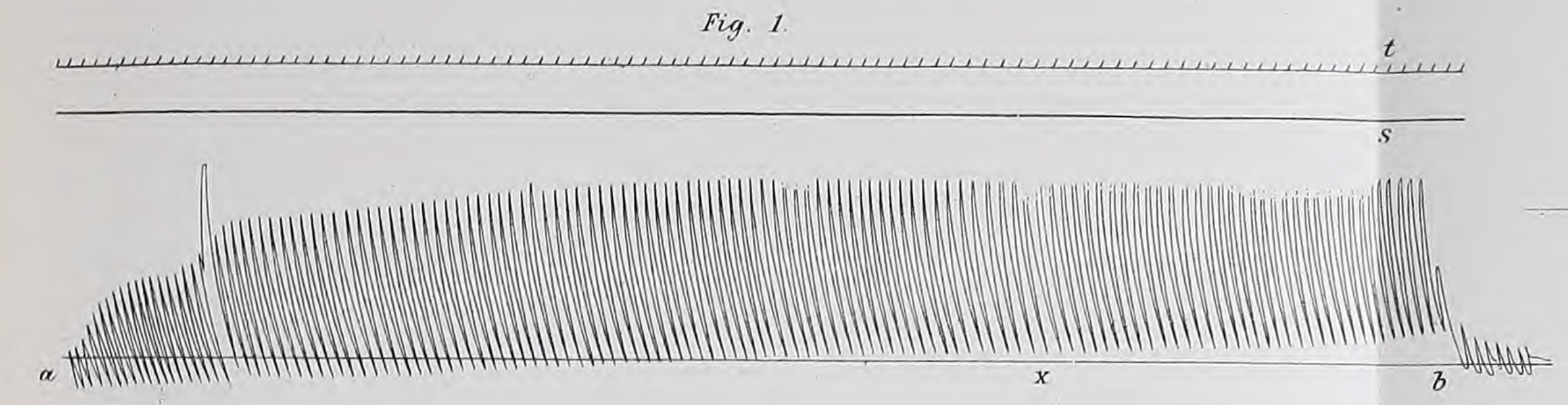
is concerned in the expression of the emotions. With powerful currents general clonic spasms, passing into general tetanus, come on. When the stimulus is applied to the deep parts of the anterior tubercles the tremor is usually absent, but the stimulation is often accompanied with violent rhythmic efforts to draw the head back; sometimes also with twitching of the ears.

The extreme feebleness of the currents which give characteristic results seems to preclude the possibility of the stimulation of neighboring parts by radiation of the currents being the cause of the phenomena. We made however several experiments with the view of excluding this possible source of error. Perfectly typical results were obtained after removal of the cerebral hemispheres and of the optic thalami and corpora striata (the latter in the cat), so that the phenomena are not due to fear or pain (which were also eliminated by the ether), or to the radiation of currents to any of those parts. Removal of the cerebellum also did not prevent the occurrence of the phenomena: after all these operations however somewhat stronger stimulation was required, doubtless on account of the diminished irritability resulting from the more severe operation. Finally we endeavoured to eliminate any result due to escape of the current to the medulla oblongata by severing the midbrain from the parts behind after finding the normal results, and then trying again the effect of the midbrain stimulation. By the severance electric continuity would not be impaired, and any part of the effect due to radiation of the current to the medulla might still be expected after it. To make the division complete without injuring the midbrain was we found no easy task, but in two cases in which *post-mortem* examination shewed that we had accomplished it, and after the animal had been allowed an hour to recover from the shock, no results followed the midbrain stimulation until the secondary coil was pushed up over the primary, giving currents of such strength that, as evinced by the contraction of the muscles in the neck, etc., they escaped in all directions. Then the chest suddenly passed into an inspiratory state, but with no signs of accelerated inspirations; the inspiratory muscles were obviously merely held in tetanic contraction by the current reaching directly the respiratory tracts in the spinal cord or medulla. Stimulation of the medulla directly by the insertion of the electrodes into it produced similar results, with general tetanus. We believe therefore that we are justified in ascribing the effects observed by us, to the stimulation of a respiration-regulating centre lying deep in the back part of the midbrain.

We had not expected to find as marked expiratory effects in the rabbit, where the expirations are mainly passive, as in the frog where they are due to active muscular contractions; and during the more or less tetanic inspiratory conditions represented in Figures 2, 3, 4, 5 and 6 it is obvious that the expiratory centre is more or less inhibited, which is perhaps all we had any reason to look for. Still we had rather expected to find some sign of a powerful expiratory effort after the cessation of the stimulation, and as a rule this was conspicuous by its absence. In many cases, however, as in Fig. 5, the chest passed rapidly towards an expiratory position during powerful midbrain stimulation, and while the inspiratory muscles were still in a state of fairly perfect tetanus. At first one might be inclined to ascribe this to exhaustion of the inspiratory muscles, but that this is not its cause is obvious from the fact that a powerful series of inspiratory movements immediately follows cessation of the stimulation: at *p*, in Fig. 5, for instance. The relaxation of the chest walls then is due in these cases in some way to the stimulation and not to muscular exhaustion. As this effect only occurred during the employment of pretty strong currents, and was moreover by no means constant, we were led to think that it might be due to the escape of the current to some inspiration-inhibiting centre, and further examination has led us to suspect that such a centre does exist deep in the front part of the medulla or in the *pons Varolii*. Fig. 7, for example, gives the results of stimulations with the uncovered points of the electrodes lying in the pons, and it will be seen that in each case the effect was of an inspiration-inhibiting character. The stimulation was accompanied by general convulsions when the secondary coil was at 16 and 14. We have not however had yet the opportunity to pursue this point further, and the effect may perhaps be due to a direct action upon the respiratory centre in the medulla.

During prolonged feeble stimulation of the midbrain (2-5 minutes) the chest never passes in the manner above described as sometimes occurring during stronger stimulation, into the expiratory position, the effect of the stimulation gradually dying away and the respiration becoming normal, except for the dyspnoëic alterations due to the conditions of the experiment.

The tracings in Fig. 8 were taken from a cat, the cerebrum of which was removed; the electrodes were inserted in the posterior corpora quadrigemina, and it will be seen that the results of the stimulations (secondary coil at 20 and 21) are identical with those obtained from the rabbit.



XII.

ON THE RESPIRATORY FUNCTION OF THE INTERNAL INTERCOSTAL MUSCLES.

BY H. NEWELL MARTIN AND E. M. HARTWELL.

With Plate 14.

[*Journal of Physiology*, Vol. II, 1879. Reprinted in *Studies from the Biological
Laboratory of the Johns Hopkins University*, Vol. II, 1880.]

An inspection of the ordinary text-books of Physiology is sufficient to shew that the part played by the internal intercostal muscles, in the production of the respiratory movements of the mammal, is still a subject upon which there is no agreement among Physiologists. Thus in the text-books accessible to us we find these muscles, in some cases with more or less reserve, described as inspiratory in function (Dalton, Ludwig, Vierordt); or as both inspiratory and expiratory in different portions (Carpenter, Flint, Hermann, McKendrick); or as expiratory only (Donders, Funke); while Foster says that their action must at present be left an open question. This divergence of opinion induced us to attempt to solve the problem by a method which, so far as we know, has not hitherto been employed.

To arrive at a decision as to the function of these muscles as rib elevators or rib depressors, from a simple mechanical study of their attachments seems impracticable; on account of the irregular shape of the ribs and the doubt which must exist as to whether the upper or the lower rib, to which one of these muscles is fixed, is to be regarded as its origin or insertion. Moreover, if experiments be made in which any or all of the other muscles be cut away, then direct observation of the movement of the ribs which follows when the internal intercostals contract is useless so far as settling their function goes; because we do not know that we have not removed some muscles which, in ordinary breathing, held fast either the upper or lower rib and so determined either the inspiratory (rib elevating) or the expiratory (rib depressing) function of the muscle. The observation of the result of direct electrical stimulation of these muscles is also not decisive: unless all the other

muscles which work with them in breathing be also excited in proper order and degree; which is impossible. Unless this be done, however, we cannot by this means tell which rib is normally the fixed one, when one of these muscles contracts. It seemed to us, however, that, by isolating an internal intercostal and then observing whether it contracted simultaneously or alternately with the diaphragm, its function could be settled; since, from the general co-ordination of muscular contractions in the respiratory movements, there can be no doubt that muscles excited from the respiratory centre and contracting during respiration simultaneously with the diaphragm, are inspiratory muscles; and that those contracting when it relaxes, are expiratory.

Dogs and cats were employed in our experiments. The animals having been etherized, tracheotomy was performed and the apparatus for artificial respiration connected with the wind-pipe. The abdomen was opened by an incision along the *linea alba* and a transverse incision, so as to expose the diaphragm from below. The skin and the serratus and pectoral and other muscles were then dissected away from one side of the chest so as to lay bare the external intercostal muscles from the fourth or fifth to the ninth or tenth ribs: except where they were covered at their dorsal portions by the muscles running alongside of the vertebral column. During this operation several small vessels commonly required tying, especially in the dog.

One intercostal space, say that between the eighth and ninth ribs, was then selected and the anterior part of the external intercostal muscle divided, near its attachment to the lower of the two ribs, for from an inch to an inch and a half at its sternal end. The internal intercostal, which was carefully avoided during the operation, then remained alone, with the pleura uniting the front parts of the two ribs. The eighth and ninth costal cartilages and the tissues between them were next divided, the chest opened and the artificial respiration apparatus set at work. The tissues in the seventh and ninth intercostal spaces were then completely divided nearly all the way back to the vertebral column.

Next, from the pleural side, a fine-bladed knife was inserted between the eighth intercostal nerve and the eighth rib near the vertebral column and an incision carried forwards, without cutting the nerve, until it reached the outer end of the region where the external intercostal muscle had been divided. In making this incision we have found it impossible to avoid cutting the intercostal vein of the space operated upon; the artery was sometimes divided also, but this did not seriously impair the result.

An incision of similar extent was then made along the upper border of the ninth rib, and finally a bit of both ribs corresponding in extent and position to these incisions was completely cut away by bone forceps. By this means we obtained from an inch to an inch and a half of the sternal ends of the eighth and ninth ribs, united only by the internal intercostal muscle and the pleura, and connected with the rest of the body by a band of tissues consisting of the intercostal nerve (and artery) and some muscle and pleura.

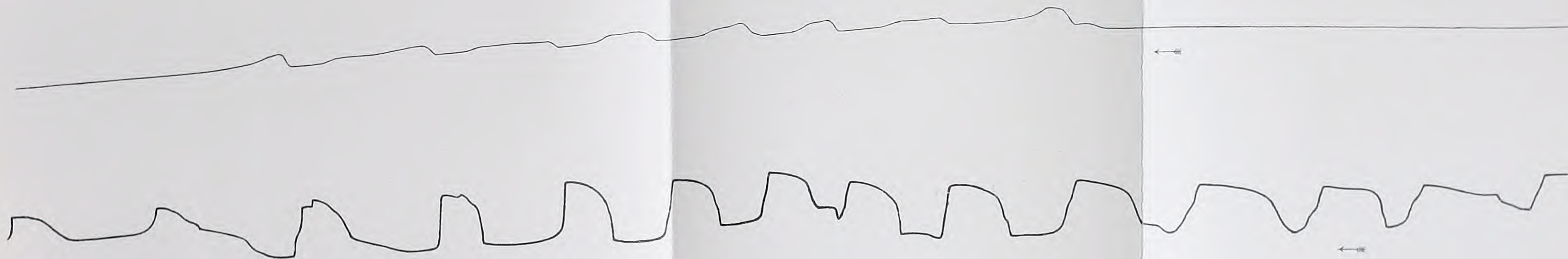
The remaining sternal piece of one of the ribs, sometimes the upper, sometimes the lower, was then fixed in a clamp and placed in such a position that the band of tissues above referred to hung quite lax; so that movements of the ribs or even of the whole trunk, unless unusually powerful, could not, through it, drag on the piece of muscle to be experimented upon. A string was then attached to the other rib and passed over a pulley to a lever which carried a weight and extended the muscle. This lever carried a pen which wrote on the paper of a Ludwig's Kymographion. A tambour was fixed beneath the diaphragm and connected with another. This latter tambour was provided with a lever which recorded the contractions of the diaphragm immediately under the lever connected with the intercostal muscle.

The artificial respiration was then stopped, and the animal was generally found apnœic. The further course of events differs in the dog and cat. In the former the diaphragm, when the apnœa passed off, made a few contractions without any activity of the intercostal muscle; but this latter soon began to contract in regular alternation with the diaphragm and before the occurrence of expiratory convulsions; in fact with the commencement of dyspnœa. Having made a few contractions, varying in number from fifteen to five or six, it again ceased its activity, although the animal became more and more dyspnœic as evinced by the contractions of the diaphragm. This cessation seems due to the exhaustion of the muscle occurring rapidly from exposure and the interference with its blood supply; since the contractions become successively feebler before disappearing; and if artificial respiration be resumed and the animal kept alive until the muscle has had a period of rest, then on again stopping the respiration the phenomena are repeated, but the muscle makes a smaller number of contractions. We have seen this restoration occur five times in the same dog. The figure, Plate I [Plate 14 of this volume], to be read from right to left, shews the tracing of the fourth set of contractions obtained in one experiment with the sixth internal

intercostal muscle of a dog; the ascents of the upper line indicate contractions of the intercostal muscle; and those of the lower line contractions of the diaphragm. It will be seen that they alternate perfectly. In order to get accurate tracings, we have found it necessary to divide completely the straight and oblique muscles of the abdomen: otherwise the action of these in dyspnœa, as expiratory muscles, when pulling down the ribs is apt to compress the abdomen and falsify the record of the tambour beneath the diaphragm. In order to see the phenomenon, however, it is not necessary to have any recording apparatus at all: the alternating contractions of the diaphragm and the intercostal muscle can be readily observed directly: and the latter occur in greater vigour no doubt from the absence of the shock due to the extensive abdominal incisions and the exposure of the viscera.

In the cat the internal intercostal muscle rarely contracts until the occurrence of expiratory convulsions: but during these it contracts very powerfully when the diaphragm is most completely relaxed. While the convulsions occur, it is necessary to hold the vertebral column of the animal very firmly in order to prevent any drag on the intercostal nerve. Usually the muscle is exhausted during these contractions; but on these convulsions passing off we have sometimes seen it in action alternately with the first few of the slow final contractions of the diaphragm; its contraction occurring immediately after the diaphragmatic, and being followed by a shorter or longer pause before the next diaphragmatic contraction began.

In some experiments the strip of muscle used was the portion between the costal cartilages; which is not covered by the external intercostal. The results thus obtained were the same as when a portion lying between the bony ribs was employed. The results of our experiments, we believe, shew decisively that the internal intercostal muscles are expiratory in function throughout their whole extent; at least in the dog and cat: and that in the former animal they are almost "ordinary" muscles of respiration, coming into play very early in dyspnœa, while in the latter they are "extraordinary" respiratory muscles, only active during extreme dyspnœa; unless the later action be ascribed to a diminution of the irritability of the muscle, brought about by the unnatural conditions to which it was exposed, which may, perhaps, influence more quickly the thinner muscles of the cat than the thicker ones of the dog.



XIII.

SOME OBSERVATIONS ON THE EFFECT OF LIGHT ON THE PRODUCTION OF CARBONDIOXIDE GAS BY FROGS.

BY H. NEWELL MARTIN AND JULIUS FRIEDENWALD.

[*Studies from the Biological Laboratory of the Johns Hopkins University,*
Vol. IV, 1889.]

The influence exerted by light on the metabolisms of the animal body has been recognized for some fifty years. The first thorough and carefully executed work on this subject was published by Moleschott.* That writer concluded from a large number of experiments on frogs, that these animals expire, under similar temperature conditions, $\frac{1}{12}$ to $\frac{1}{4}$ more carbondioxide in the light than in the dark; that the greater the intensity of the light, the greater the quantity of carbondioxide produced; and furthermore, that this action of the light is effected not only through the eye but also through the skin. Since the publication of Moleschott's work, many observers have investigated this phenomenon. In general the conclusion has been reached that animals of the same species, kept at uniform temperature, expire for each gram of body-weight more CO₂ per hour in light than in darkness, and that the quantity of carbondioxide produced varies with the temperature, the intensity and color of the light, and the species of animal employed.

As it had been demonstrated that the increase in the production of carbondioxide brought about by light is effected mainly through the optic nerve, we endeavored to determine during the months of February, March, April and May whether this action is merely reflex, or whether it depends on psychical conditions in which the cerebral hemispheres are concerned. For this purpose the cerebral hemispheres of a dozen frogs of the species *Rana Catabiana* (nearly all of the frogs weighed over 100 grams) were removed, care being taken to avoid touching or in any way injuring the optic nerves. The frogs were then put aside and carefully watched until the wounds had healed. None of the frogs were used in any of our experiments until a month after the operation had been per-

* Wiener Med. Wochenschrift, 1855.

formed, at a time when all traumatic inflammation had passed off. In every case a post-mortem examination was made to determine whether the optic nerves had been cut or injured.

The apparatus used for measuring the quantity of carbondioxide produced was in the main similar to that employed by Moleschott. The frogs were placed within a bell-jar, the bottom of which was immersed in a shallow vessel containing mercury. The air led to the bell-jar passed through a flask containing a strong solution of caustic potash, connected with which was a U-tube filled with caustic potash, which led to a similar U-tube communicating with the bell-jar. Connected with the exit side of the bell-jar was a flask containing concentrated sulphuric acid, followed in turn by a U-tube containing bits of calcium chloride, a weighed caustic potash U-tube, a weighed Geissler's bulb with its caustic potash, two more weighed caustic potash U-tubes, another calcium chloride U-tube, a flask containing a solution of barium hydrate, another calcium chloride tube, and finally an aspirator. The air, freed of all carbondioxide, entered the jar containing the frogs. From here the carbondioxide given off by the frogs passed through the sulphuric acid and calcium chloride, where it was freed of all moisture, and thence entered the weighed caustic potash tubes, by which it was absorbed. The baryta bulb placed beyond these tubes to indicate whether all the carbondioxide had been absorbed by the caustic potash tubes never showed the slightest trace of a precipitate. All the connections were hermetically sealed, so that no air could enter nor gas escape except through the regular channel, and tests were made in this respect until we were confident that this end had been attained. The apparatus was placed in the "dark room" of the biological laboratory, which could be made perfectly dark or moderately illuminated at pleasure. The caustic potash bulbs having been carefully weighed, the frog was weighed and placed under the bell-jar, the aspirator was started and the current of air regulated, and thus the experiment began. Each experiment lasted twelve hours, and hourly the temperature of the room was taken and an average made. After the experiment the caustic potash bulbs were again weighed, and from the weight of the animal and the weight of the carbondioxide given off, the quantity of carbondioxide produced was calculated for twenty-four hours for each hundred grams of frog.

The first experiments were performed with normal frogs, and Moleschott's conclusion was confirmed that these animals expire more carbondioxide in the light than in the dark. The actual figures are given in

the subjoined table. Twenty-six experiments (13 of which were in the light and 13 corresponding ones in the dark) were performed on frogs deprived of their cerebral hemispheres. Of these it will be observed that in only two instances (experiments Nos. 4 and 7) was there an excess of carbondioxide obtained in the dark; and as the frogs used in these instances were very small, weighing respectively 44 and 42 grams, it can readily be understood how an error might arise in dealing with the very small quantities of carbondioxide given off by these frogs. In all other instances the quantity of carbondioxide was found to be greater in the light than in the dark. All experiments bracketed together were performed on the same frog, and it is worthy of mention that much less carbondioxide was given off on rainy or cloudy days in the light than on bright days. Thus in experiments 14, 15 and 16 we find the figures 848 and 852 on bright days, while 678 was obtained on a cloudy day.

It is also interesting to note, that comparing the quantities of CO₂ obtained from frogs with their hemispheres removed with those obtained from normal frogs, we find that most of the former figures fall within the maximum and minimum limits of the latter. Making the same comparison of the former figures with those obtained from normal frogs by Moleschott, all of the latter also fall within those limits; from which we may conclude that the cerebral hemispheres exercise no control on the oxidations in the frog's body.* This is well shown in experiments 2, 3 and 11, in which the same frog was used. This frog was normal in experiments Nos. 2 and 3, and afterwards its cerebral hemispheres were removed.

Our next endeavor was to determine whether, in frogs deprived of their cerebral hemispheres, the light acts only through the eye or also partly through the skin. For this reason a frog was blinded by removing its eye-balls, and the quantity of carbondioxide given off in the light and dark determined. From a glance at the table it is evident that under these conditions a greater quantity of carbondioxide was obtained in the light than in the dark, although our differences in this regard are not as great as those obtained by Moleschott. This less difference may be due to the fact that our frogs when exposed to light were in a room with walls painted black, and therefore not very brightly illuminated.

As a result of our experiments we believe we are justified in concluding that in frogs deprived of their cerebral hemispheres a greater

* Corin and Beneden came to a similar conclusion, working on pigeons. Archives de Biologie, Tome VII, Fasc. II, 1887.

quantity of carbondioxide is given off in the light than in the dark; that therefore the influence of light in producing greater oxidations in normal frogs is simply reflex, and not due to greater bodily activity brought about by psychical conditions dependent on the light; that the cerebral hemispheres do not take any direct part in regulating the oxidations of the frog's body; and that this reflex action of the light, though mainly effected through the eye, is produced partly also through the skin.

TABLE.

No. of Experiment.	Date.		Temperature °C.		Quantity of CO ₂ in mgr. given off in 24 hours for 100 grams of frog.		
	Light.	Dark.	Light.	Dark.	Light.	Dark.	
1	Feb. 23	Feb. 24	18.4	18.9	764	722	} Normal frogs.
2 {	" 28	" 29	19.2	20.	678	440	
3 {	March 1	March 2	19.3	20.	652	428	
4	" 5	" 6	19.5	20.2	426	442	} Frogs deprived of their cerebral hemispheres.
5 {	" 8	" 9	20.6	19.2	766	658	
6 {	" 12	" 13	18.5	21.5	798	648	
7	" 15	" 16	20.	20.5	400	422	
8 {	" 19	" 20	18.8	17.5	724	524	
9 {	" 22	" 23	17.9	17.4	680	534	
10 {	" 26	" 29	18.6	21.5	592	423	
11 {	April 3	April 5	19.5	19.	590	438	
12	" 10	" 12	17.6	18.9	344	338	
13	" 17	" 19	17.83	18.	682	436	
14 {	" 24	" 26	18.45	24.63	848	708	} Frogs deprived of their cerebral hemispheres and also blinded.
15 {	May 1	May 3	17.16	20.02	852	696	
16 {	" 8	" 10	24.41	24.50	678	656	
Average,					644	533	
or as					1.20	: 1	
17 {	May 20	May 19	18.	18.5	820	792	} Frogs deprived of their cerebral hemispheres and also blinded.
18 {	" 21	" 20	18.5	19.3	846	798	
19 {	" 22	" 21	19.5	19.6	826	790	
Average,					830	760	
or as					1.09	: 1	

XIV.

PRELIMINARY ACCOUNT OF EXPERIMENTS IN REGARD TO THE CIRCULATORY AND RESPIRATORY CHANGES OBSERVED IN ANIMALS PLACED IN THE PNEUMATIC CABINET.*

BY H. NEWELL MARTIN AND F. DONALDSON, JR.

[*The New York Medical Journal*, May 15, 1886.]

The great objection to the use of the pneumatic cabinet has been, beyond doubt, that we had no knowledge of the physiological effect of rarefied and compressed air applied under these conditions on the respiration and circulation; and, indeed, I found myself so timid and embarrassed in its every-day use that I determined to submit no person further to treatment by pneumatic differentiation until I had got at its physiology. I was, therefore, very glad to take advantage of Professor Martin's suggestion that we should conduct a series of experiments upon animals placed in the pneumatic cabinet. The results of these experiments are given very briefly below. A more detailed account of them with illustrations showing the changes in blood-pressure, pulse and respiration actually observed, will appear hereafter. Our experiments have been made on rabbits, and have so far had reference only to changes in arterial pressure, in pulse-rate, in respiratory rhythm, and in the extent of respiratory movements when the air within the cabinet is rarefied or condensed.

The rabbits were chloralized, and a glass tube was placed in the trachea. From the glass tube a rubber tube led to a T-piece. From one limb of the T-piece a tube led to a Marey's tambour, which recorded on the kymograph paper the rate and extent of the breathing movements. To the other limb a tube was attached through which the animal inspired and expired. In some cases this tube opened outside the cabinet and the animal took air into its lungs under the normal atmospheric pressure. In other cases the breathing-tube opened inside the cabinet, and the animal breathed rarefied or condensed air as the case might be.

* Read before the American Climatological Association, May 10, 1886.

A cannula placed in the femoral artery recorded on the kymograph paper the arterial pressure and pulse-rate. Another manometer, placed in communication with the interior of the cabinet, recorded the variations of atmospheric pressure within it. A fourth pen was connected with the clock, and recorded seconds of time on the paper. We are enabled to state our results as follows:

I.—When the animal is breathing air from outside the cabinet, rarefaction of air within the cabinet causes a marked fall of general arterial pressure, but has no influence on the pulse-rate. The fall of pressure lasts a short time only (ten to twenty seconds), and is followed often by a temporary rise above the normal.

II.—This fall of systemic arterial pressure depends on two factors: greater flow of blood to the skin when the air around the animal is rarefied, and greater accumulation of blood in the lungs when they are distended.

III.—Of these two factors, accumulation of blood in the lungs is the more effective; for, if the animal breathes air from the cabinet and not from outside, rarefaction of air within the cabinet (in this case accompanied by no special expansion of the *thorax*) has but a trivial effect in lowering arterial pressure.

IV.—When the animal is breathing external air, rarefaction of the air within the cabinet usually has no effect upon the respiratory rate or the extent of individual respiratory acts, unless the fall of blood-pressure is considerable. If it is considerable, symptoms of anæmia of the *medulla oblongata* are seen. In most cases there is more forcible dyspnœic breathing; in some there are dyspnœic convulsions similar to those which occur when an animal is bled to death, and due to the same cause, viz., deficient blood-flow to the respiratory centre.

V.—The rapid recovery of general arterial pressure, while the animal is still in a rarefied atmosphere but breathing external air, is probably due to excitation of the vaso-motor centre, which, as is well known, is excited whenever its blood-supply is defective.

VI.—The brain, inclosed in a rigid box, which is practically unaffected by variations in atmospheric pressure, has its circulation more disturbed in the pneumatic cabinet than any other organ except the lungs.

VII.—Compression of the air within the cabinet, while the lungs are in communication with the exterior air, causes a considerable but transient rise of blood-pressure. This is probably mainly due to the forcing of blood from the cutaneous vessels; but we have not yet had opportunity to thoroughly investigate this point.

VIII.—Compression of air within the cabinet, while the lungs are in communication with the exterior air, slows the pulse as the arterial pressure rises. This is probably due to excitation, by increased intra-cranial blood-pressure, of the cardio-inhibitory centre; but further experiments are necessary before this can be positively stated.

IX.—In certain cases, when the air within the cabinet is rarefied and the animal is breathing external air, the respiratory movements cease altogether for several seconds. As to the cause of this physiological “apnœa” we are not yet ready to form an opinion. It may be due to the extra accumulation of air in the alveoli of the lungs, or to distension of the lungs exciting those fibers of the pneumogastric which tend to check inspiration.

Such, in brief, being the physiological effect of rarefied and compressed air as applied in the Ketchum cabinet, how should this knowledge affect the practical use of this apparatus? It having been found that even very great rarefaction of the air in the cabinet produces but slight effect on the circulation, provided the animal is breathing the air within the cabinet, I conclude:

1. That rarefaction of the air when the person first enters the cabinet (as directed by Mr. Ketchum), in order that the residual air may expand and so drive out any plugs of mucus in the lungs, may be done without danger to the individual. In view of the great and sudden fall of arterial pressure when the animal is breathing outside air and the air within is rarefied, I conclude:

2. That the air in the cabinet should never be suddenly rarefied, and that the motion of exhaust should invariably be slowly made, and the amount of rarefaction small, particularly at the first treatments. This sudden fall of arterial pressure depending as it does upon an increased blood-flow to the skin and an accumulation of blood in the distended veins and lung alveoli, I conclude:

3. That, before deciding a person to be a proper subject for treatment by pneumatic differentiation, *thorough examination* should be made of the *heart*; and that no person found to have pronounced insufficiency or stenosis of the mitral valve or the slightest tricuspid regurgitation should, under any condition, be placed in the pneumatic cabinet; for it is plain that rarefaction of the air would be most dangerous in such cases. The fall of arterial pressure would seem to depend chiefly upon the accumulation of blood in the lungs, for, if the animal breathes air from the cabinet and not from outside, rarefaction of air within the cabinet has but a trivial effect upon arterial pressure. From this fact I conclude:

4. That the liability to pulmonary hemorrhage is very slight, though greater perhaps than Dr. Williams has supposed. It having been proved that compression of the air within the cabinet while the animal breathes external air causes a considerable rise in arterial pressure, and slows the pulse from the increase of intra-cranial blood-pressure, I conclude :

5. That old persons, with possibly atheromatous arteries, are not, generally speaking, proper subjects for the pneumatic chamber, especially where their trouble is emphysema or asthma, and compression of the air within the cabinet is made use of in order to assist expiration.

Again, in view of the sudden and pronounced fall in arterial pressure following rarefaction, and of the considerable though transient rise of the same following compression of the air in the cabinet, I conclude that the method of differentiation should be practiced with much care and discrimination in all cases, and that the actual movements of exhaust and compression should be made always very slowly and gently.

Finally, the Ketchum cabinet should be in the hands of careful auscultators only, for in those of the inexperienced or careless great harm may be done.

XV.

SOME EXPERIMENTS AS TO THE PHYSIOLOGICAL EFFECTS OF "DIFFERENTIAL RESPIRATION."

BY H. NEWELL MARTIN AND G. P. DREYER.

With Plate 15.

[*Studies from the Biological Laboratory of the Johns Hopkins University,*
Vol. V, 1893.]

Some years ago there was put before the medical profession a method of treating pulmonary diseases, especially phthisis, by the use of a so-called "*pneumatic cabinet*." This cabinet was so arranged that while the patient breathed ordinary atmospheric air under normal atmospheric pressure, the air which surrounded him could be rarefied or compressed at will, and thus an abnormal expansion or an abnormal compression of the thoracic and abdominal cavities be brought about with each respiration. The name "differential respiration" was given to this process, and it was widely advertised by the patentee of the "cabinet." What the physiological effects of breathing under such very unusual conditions might be seemed a question of sufficient importance to justify a careful experimental investigation.

The phenomena produced by breathing rarefied air and by breathing compressed air had been studied, but here was a new problem, namely, the results of breathing air under normal pressure while the whole surface of the body was exposed to air under abnormal pressure. One of us, soon after the "pneumatic cabinet" was put on the market, made some experiments in conjunction with Dr. F. Donaldson, Jr.,¹ which proved that the pneumatic cabinet should be used with great caution, since when the air in it was only moderately rarefied, fainting was produced in healthy rabbits. Dr. Donaldson's departure from the city brought the investigation to a close before any thorough research had been made, and in this paper we give some of the results of a prolonged research which is not yet concluded. For the present we shall deal only with the effects of rarefaction of surrounding air on an animal breathing air under normal pressure.

The pneumatic cabinet supplied to physicians was unnecessarily heavy and cumbersome for use with rabbits and cats, so we had to plan something more suited to our purpose. To get a perfectly air-tight box we found much more troublesome than we had anticipated, but we finally devised the apparatus described below, which has proved quite satisfactory.

It consists of a rectangular iron box 90 cm. long, 40 cm. high and 35 cm. wide, completely open on one of its long sides which will be spoken of as the top. It can therefore be cast in one piece, as was the case with our box whose walls are somewhat less than 1 cm. thick.

The free edge of the box extends horizontally outwards to the extent of 3 cm. in the form of a ledge running around the four sides, the upper surface of this ledge being planed so as to fit accurately against a corresponding surface of the lid of the box to be described presently.

Over an area of about 15 cm. square in the middle of one end of the box the wall is made two or three times as thick as elsewhere, and here a number of openings are drilled to establish communication with the outside.

A detailed description of the lid which is necessary to complete the cabinet is impossible without the use of diagrams. Suffice it to say that it too was made of cast iron, but instead of a continuous sheet of metal, consists only of a frame which may be compared to a window-sash divided by two cross-bars into three sections, each of which is occupied by a pane of heavy plate glass. In this way light may penetrate the box and enable one to observe the animal during the course of an experiment.

The frame of the lid presents a flat planed under-surface with which it rests on the upper surface of the ledge of the box spoken of above. Between these two surfaces, moreover, there is placed a sheet of pure rubber $\frac{1}{2}$ cm. thick and 3 cm. wide, effectually preventing all leakage at this point when the lid was screwed down. For this purpose strong bolts were used at intervals of 15 cm. around the four sides, the bolts passing from below upwards through the ledge of the box, the rubber pad and the cover. The square heads of the bolts prevent them from turning when the nuts are tightened up by hand. To close the box, therefore, after the animal is introduced, the lid is placed in position, the bolts to the number of about 20 inserted and the nuts screwed on. This method of closing the box may seem very objectionable at first sight on account of the apparently great expenditure of energy and time which it involves. In reality, however, one soon learns to do it rapidly and with-

out much trouble; we found that it took us only from 2 to 3 minutes, as a rule, to put the animal in the box, make all the necessary connections and screw down the lid. Moreover, in most of the experiments, when once closed, the lid remains in position until the experiment is finished. Where the nature of the experiment requires frequent opening of the box it becomes a more serious matter. More convenient methods for fastening down the lid were tried, but none of them succeeded in rendering the box completely air-tight.

A number of openings in one end of the box were spoken of above. By means of one of these holes communication is established between the outer air and the trachea of the animal, in this way supplying air under normal atmospheric pressure after closure of the box, at the same time providing the means for continuing the application of ether when desired. A second opening was required for the connection between the blood-pressure manometer of Ludwig's kymograph and the carotid artery. The interior of the cabinet communicated by another opening with a second mercury manometer, by means of which a continuous record of the air-pressure in the box throughout the experiment is obtained on the kymograph paper (see Plate XII [Plate 15 of this volume] *MN*). Finally the cabinet was connected with a three-way stopcock, by means of which its interior could be put in communication on the one hand with the outside air, or else with an air-chamber of about 75 litres capacity. This reservoir was exhausted with an air-pump before the experiment began, and so enabled us by simply turning the stopcock to rarefy the air in the cabinet quickly to the desired extent. On reversing the stopcock the air rushed into the cabinet again, and this process could be repeated a number of times. The pens of the two manometers already mentioned, and a time-marker indicating seconds, are arranged so as to write in the same vertical line.

The experiments described below were made on etherized cats, ether being an anæsthetic which could be easily renewed during the experiment whenever necessary, on account of the communication of the trachea of the cat when in the box with the exterior as described above. It has already been mentioned that the blood pressure was taken from the carotid artery, especially because it was intended to cut the pneumogastrics in many cases, and one operation served both purposes.

In general, the anæsthetized animals stood the experiment so well that the rarefaction could be repeated six or more times.

We give below in tabular form the detailed results of six experiments, as a basis for discussion as to the general outcome of our work.

TABLE I.

Time.			Pressure in Case.	Blood Pressure.	Pulse.	Cat.
H.	M.	S.				
3	9	50	Normal.....	177 mm.	267	II
	10		Rarefaction of 1.2 cm. of mercury	136	282	"
		10		146	282	"
		20	Return to normal	166	255	"
	11	40	Normal.....	160	243	"
		50	"	160	244	"
	12		Rarefaction of 3.4 cm	58	255	"
		10	"	130	264	"
		20	"	98	264	"
		30	"	111	249	"
		40	"	105	246	"
		50	"	111	244	"
	13		"	114	234	"
2	59	40	Normal.....	137	231	III
		50	"	137	228	"
3			Rarefaction 1.5 cm	80	(?)	"
		10	"	124	261	"
		20	"	124	249	"
		30	"	127	252	"
		40	"	128	255	"
		50	"	128	252	"
	1		"	133	240	"
		10	"	135	231	"
		20	"	137	219	"
		30	"	140	210	"
3	53	10	Normal.....	142	185	XXII
		20	"	142	189	"
		30	Rarefaction 1.4 cm.....	82	192	"
		35	"	122	228	"
		40	"	130	204	"
		45	"	112	192	"
		50	"	103	180	"
		55	"	99	180	"
	54		"	96	168	"
3	21	40	Normal.....	210	234	XXIV
		50	"	208	231	"
	22		Rarefaction 1.4 cm... ..	145	252	"
		5	"	141	240	"
		10	"	138	240	"
		15	"	126	228	"
		20	"	120	240	"
		25	"	113	222	"
		30	"	105	217	"
		35	Return to normal			
	26	40	...	160	174	"
		50	...	157	168	"
	27		Rarefaction .6 cm.....	116	168	"
		5	...	117	180	"
		10	...	118	180	"
		15	...	118	180	"
		20	...	118	180	"
		25	...	117	168	"
		30	...	115	168	"

Time.			Pressure in Case.	Blood Pressure.	Pulse.	Cat.
H.	M.	S.				
2	11	40	Normal	148	192	X
		50	"	147	195	"
12			Rarefaction 2.7 cm.....	24	237	"
	10		" "	86	231	"
	20		" "	72	212	"
	30		" "	69	210	"
	40		" "	78	213	"
	50		" "	95	210	"
19	40		Return to normal	129	168	"
	50		"	127	168	"
20			Rarefaction 5.7 cm.....	40	no pulse	"
	10		" "	"
	20		" "	"
	30		Return to normal			
	40		"	70	188	"
	50			136	207	"
				etc.	etc.	
3	53	45	Normal	145	177	XXVI*
		50	"	144	180	"
		55	"	144	174	"
54			Rarefaction 1.2 cm.	80	183	"
	5		" "	83	180	"
	10		" "	84	180	"
	15		" "	81	180	"
	20		" "	80	174	"
	25		" "	80	171	"
	30		" "	81	171	"
	35		" "	82	171	"
	40		" "	83	174	"
	45		Air let in	136	171	"

* This portion of the table was compiled from the tracing given in Plate XII [Plate 15 of this volume].

The table shows that the amount of rarefaction employed varied considerably; the extremes being 5 mm. and 5.5 cm. of mercury pressure.

No graphic record was taken of the respiratory movements of the animal, but direct observation showed that in nearly every case a rarefaction equaling 1.5 cm. mercury pressure caused a resistance that the expiratory muscles could not overcome. When the air surrounding the animal was rarefied to this extent, expiration became impossible, the muscles could not overcome the resistance opposed to them.

Rarefaction exceeding 1.5 cm. of mercury pressure caused a deep initial inspiration, and then the thorax remained expanded as long as the rarefaction was maintained: the animal was in a condition of *mechanical* apnoea.

* The tables also make it clear that a difference of but 6 mm. of mercury between the intra-pulmonary and extra-thoracic pressures is sufficient to set up marked circulatory disturbances, involving both arterial pressure and pulse-rate. The variations in arterial pressure due to rarefaction of the air were always similar, though varying much in degree. *Whenever extra-thoracic atmospheric pressure is lessened, blood pressure falls*, if the lungs be still supplied with air under normal atmospheric pressure.

This is illustrated by many cases given in the foregoing table, *e. g.*:

Rarefaction.	Arterial Pressure.	
0.6 cent. Hg	falls	40 mm. of Hg.
1.4 " Hg	"	60 " "
2.7 " Hg	"	120 " "
5.7 " Hg	"	177 " "

In the last of the above cited examples, arterial pressure in the carotid was 40 mm. below the zero or base line of the manometer, indicating an actual suction of blood from the systemic arteries, causing a negative pressure in them.

As a rule, partial recovery takes place from the first sudden fall of arterial pressure, but this is but transient and never brings arterial pressure back to what it was before the rarefaction; and during the rarefaction, continued in some cases for four minutes, arterial pressure always remained below the normal.

In Plate XII [Plate 15 of this volume] is given a copy of a tracing showing the effect of extra-thoracic rarefaction on arterial pressure; the sudden fall, temporary recovery, and the final permanent lowering.

In attempting to explain this great and sudden fall of pressure we had to consider observations by Paul Bert and recorded in his well-known book "*Pressions Barometrique.*" Bert states that at high altitudes attained quickly, as by mountain-climbing or a balloon ascent, superficial veins (those of the eyelids and lips, for example) become greatly congested, and that bleeding from the nose and eyes is apt to occur. The thin-walled and slightly muscular veins respond more quickly to diminution of external pressure than the thicker-walled, elastic and muscular arteries, and so the veins become gorged while the arteries empty. Such a filling of the venous system at the expense of the arterial must bring

about a fall of arterial pressure, unless there were compensating constriction of the arterioles.

In Bert's work the diminished atmospheric pressure influenced equally the pulmonary and systemic vessels, which was not the case in our experiments. But it is obvious that diminution of atmospheric pressure on the surface of the body while intra-pulmonary air pressure remained normal would tend still more strongly to cause dilatation of superficial veins and capillaries. But such diminution of atmospheric pressure as we used (a few millimeters or centimeters of Hg) are hardly comparable with those experienced by Glaisher and others in balloon ascents. Such a fall of arterial pressure as occurs in the "pneumatic cabinet" with a slight rarefaction of the air would be fatal to balloonists long before they reached such altitudes as those recorded by Glaisher and others; altitudes at which the barometric pressure was far lower than in any of our experiments. We found that the blood was drawn from the systemic arteries as indicated by fall of carotid pressure, and we could not account for the whole or even a large proportion of it, as gathered into the veins of the skin. Our first problem was, where did the blood go when it had been so markedly abstracted from the systemic arteries?

Our first idea was that this blood might be stored in the vessels of the abdominal viscera. The thorax and skull being relatively unyielding, and the belly walls soft, it was easy to conceive that when the pressure on the exterior of the animal's body was decreased there would be an accumulation of blood in the veins of the portal system. Accordingly, after trying the effects of two or three rarefactions on an animal and getting the usual results, we opened the case and ligatured the abdominal aorta above the origin of the coeliac axis. In this way nearly all the abdominal and more than half the general systemic blood-flow was blocked. If the fall of arterial pressure usually seen on extra-thoracic rarefaction were due to dilatation of cutaneous or abdominal veins, it must be much less after the aorta had been ligatured as above stated. But experiments showed that this was not the case. To take an example:

TABLE II.

Cat XXIV.	Time.			Normal Pressure.	Rarefaction.	Arterial Pressure.
	H.	M.	S.			
	3	54	40	"	...	179 mm.
			50	180
		55	8 cm.	148
			5	...	"	150
			10	..	"	154
			15	...	"	158
			20	...	"	162
			25	...	"	165
	3	57	40	"	...	166
			50	"	...	166
		58		...	1.8 cm.	94
			5	...	"	88
			10	...	"	82
			15	...	"	83
	4	3	40	"	...	204
			50	"	...	203
		4		"	3 cm.	76
			5	...	"	63
			10	...	"	51
			15	...	"	52
			20	...	"	52
			25	...	"	52

Comparison of these figures with those given in Table I shows that enlargement of the superficial and abdominal vessels can have little to do with the observed fall in blood-pressure. The effect of rarefaction is as marked after tying the aorta (which had been done in cat XXIV) as it was before. The question then arises, what becomes of the great mass of the blood?

S. de Jager² has called special attention to three main factors on which the cubic capacity of the pulmonary vessels depends. According to him, (1) expansion of the lungs by suction, as contrasted with distension due to forcing in air under pressure, causes enlargement of the pulmonary vessels in length and width. (2) The diameter of the smaller vessels varies with the intra-alveolar pressure, the two bearing an inverse ratio. (3) The capacity of the lung capillaries is influenced by the *absolute* and *relative* pressures on the exterior of the pulmonary arteries and the pulmonary veins. In connection with this statement one must bear in mind that the pulmonary arteries, with coats so much thicker than those of the pulmonary veins, do not on merely physical grounds yield to so great an extent under variations of intra-thoracic gaseous pressure.

Under the conditions maintained during our experiments the air surrounding the animal is rarefied, causing an unusually powerful inspiratory movement. Indeed, if the rarefaction passed a moderate limit, the thoracic walls during its continuance remained fixed in the inspiratory position. The increased inspiratory movements caused by the rarefaction, with their concomitant unusual distension of the lungs, must, if de Jager be correct, cause an increase in the volume of the pulmonary vessels. Intra-alveolar pneumatic pressure, de Jager's second factor, is lessened only while the lungs are in the act of distension, and even then (except to a very trivial extent) only when the distension is rapid, as it was in our experiments. After full lung expansion, a condition of pneumatic equilibrium is quickly attained in which intra-alveolar pressure is the same as before the distension commenced. While we might, therefore, expect increased capacity of the pulmonary vessels during extra-thoracic rarefaction with concomitant fall of systemic arterial pressure through the influence of the second factor, once the rarefaction was completed and kept uniform, we should have no reason to expect further change in general arterial pressure from this cause, except the normal ones due to heart-beat and breathing movements.

Pneumatic pressure on the pulmonary arteries and veins is, of course, a pressure of one atmosphere less the amount necessary to overcome the elasticity of the lungs; which amount depends on the extent to which the lungs are expanded in consequence of diminution of pressure on their surface. In other words, the more the lungs are distended by extra-thoracic rarefaction, the less the air pressure on the great pulmonary vessels. The pulmonary artery and vein consequently expand, with the result that the lung capillaries are filled under a lower arterial pressure and emptied against a lessened venous resistance; hence, de Jager maintains that the quantity of blood contained in the pulmonary capillaries must diminish. But when we consider the physical and mechanical differences between the coats of the pulmonary arteries and those of the pulmonary veins, it becomes clear that blood in the pulmonary artery may remain under but slight alteration of arterial pressure; while so far as such changes of extra-pulmonic pneumatic pressure can influence it the flow in the less resisting and less elastic pulmonary veins may be considerably modified. If the lung veins expand while the lung arteries remain practically of their previous calibre, the vein expansion may compensate or even over-compensate the capillary emptying, and the volume of blood in the lungs at any moment remain the same or be but little

altered; and if altered, the alteration may be in the positive or negative direction. The change in the bulk of blood contained in the lungs which could possibly be brought about by transient diminution of extra-pulmonic air pressure, must in any case be so slight as to justify us in neglecting it as a factor of any importance in the explanation of the great fall of systemic arterial pressures observed when the chest was expanded by extra-thoracic rarefaction. We have found (see Table I, Cat XXIV) that even slight diminution of the atmospheric pressure on the surface of an animal's body leads to a sudden and very great fall of pressure in the systemic arteries; this was usually followed rapidly, that is, within a few seconds, by a partial recovery of arterial pressure, succeeded very soon by return to a lower arterial pressure, but not one so low as that of the primary fall; this lowered pressure was maintained approximately uniform for a considerable time. In cases where the rarefaction was greater, the fall of blood pressure was such as to lead to rapid death; the left heart apparently received no blood to pump into the arteries, and the mercury in the manometer ceased to show pulse-beats and slowly fell to zero.

The marked primary fall we believe due to the combined influence of the first and second factors indicated by de Jager and stated above. The continued low pressure observed in the cases where the rarefaction was not such as to cause death must be mainly due to the first factor (that is, the general enlargement of the pulmonary vessels when the lungs are expanded by diminution of external pressure), since the second factor ceases to operate when the rarefaction has reached its limit in any given experiment. It would seem that just as most of the blood accumulates in the abdominal vessels after section of the splanchnic nerves, causing a marked fall in general arterial pressure, so when the chest cavity is dilated by extra-thoracic rarefaction most of the blood accumulates in the pulmonary small arteries, veins and capillaries, causing great passive congestion of the lungs and a great and often fatal fall of aortic blood pressure. When the extra-thoracic rarefaction is great, a very large percentage of the total blood in the body is held in the pulmonary vessels—a percentage which would be surprising did we not know that the normal lung vessels must in each minute transmit as much blood as all the systemic vessels, and that their area and capacity must, considering the size of the organs they traverse, be far greater than that of the vessels of any other organ.

We do not know whether attention has hitherto been called to the fact which our experiments demonstrate—the fact that the lungs can, under some conditions, lock up and hold so much blood as to prevent any of it reaching the heart, and so cause death by what has been well named “internal bleeding.” This possibility seems to deserve the attention of clinicians and pathologists.

An interesting by-result of our work came from the counting-out of pulse-rates on the kymograph tracings. The fact that, starting with normal arterial pressure, any increase of blood pressure in the *medulla oblongata* tended to slow the pulse, as well as the converse fact, that lowering of normal arterial pressure in the cranial cavity is followed by quicker pulse, is well established. But it has been generally assumed that such pulse-slowness or pulse-quickening results from the raising or lowering of an arterial pressure which started from what may be called the “base line.” In other words, given a normal intra-cranial arterial pressure, increase of it will (the nerves being intact) slow the pulse; while under like conditions, lowered arterial pressure in the *medulla oblongata* will result in a quicker pulse. Our experiments serve to show that the “base line” of arterial pressure has no absolute value. With low arterial pressure, further lowering quickens the pulse; with even abnormally high arterial pressure in the *medulla oblongata* and a corresponding slow pulse, an increase of pressure makes the heart for a time beat more slowly. We have not yet had time to make a thorough study of this question, but are inclined from the results of our work so far to believe that (the nervous system being intact) no matter how low blood pressure may be, provided that it is sufficient to maintain life, a lessening of it will temporarily quicken the heart-beat; and, on the other hand, no matter how high arterial pressure may be, an increase of it will for the moment slow the pulse. There seems to be no fixed “norm” above which increased arterial pressure slows, below which decreased arterial pressure quickens the pulse: be the existing pressure what it may, increase of it slows, diminution of it quickens. We can as yet make this assertion only provisionally: though the countings of the great majority of our tracings lead us to believe it correct, we have found many exceptions, and these have to be accounted for. Possibly the dose of anæsthetic may explain the discrepancies: it was not observed with any attention during our work; as all we cared for in that connection during our pneumatic experiments was that the animal should be unconscious, and this side issue arose only after their completion and when the pulse-tracings were counted and compared.

DESCRIPTION OF PLATE XII [Plate 15 of this volume].

In Plate XII [Plate 15 of this volume] is given an exact copy of the tracing obtained from cat XXVI before, during, and after the first rarefaction of the air in the chamber. The corresponding figures have already been given in Table I.

The curves are to be read from right to left.

The blood pressure tracing is shown in AB , the base line or line of no-pressure being the straight line CD .

MN shows the condition of the pressure in the case, being the normal atmospheric pressure from M to O . The rarefaction is indicated by the descent of the line at O , and was maintained to the point P , where the air was again admitted and the pressure returned to the normal.

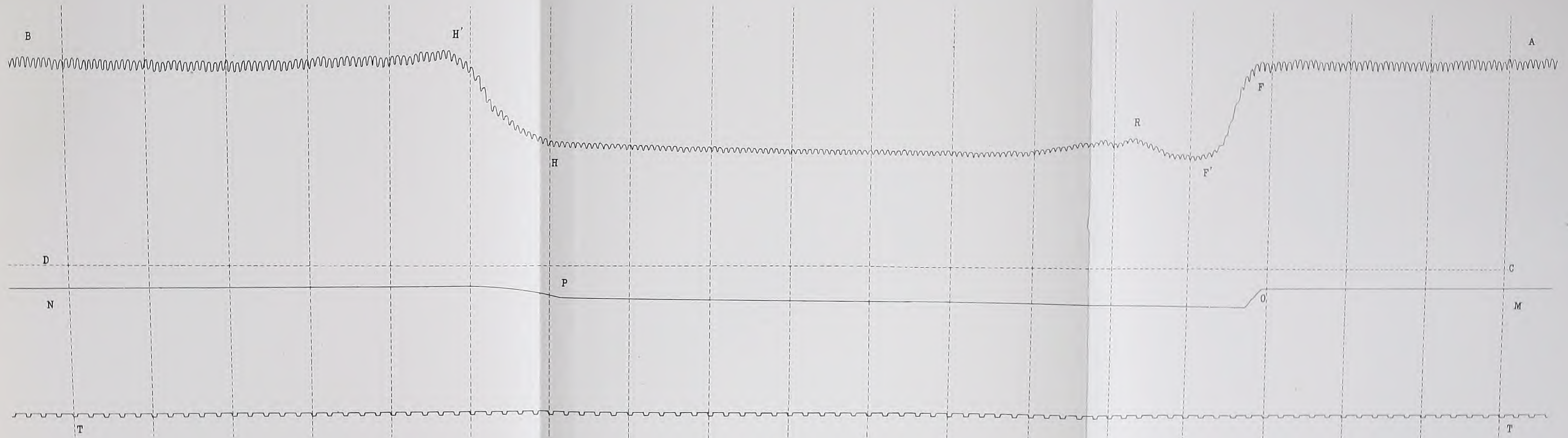
TT' gives the tracing of a Martin pen, the time intervals marked on it being seconds.

The vertical lines were used to count the pulse rate at intervals of 5 seconds, and were retained in the proofs for convenience of verification.

The blood pressure tracings show the initial fall of pressure at FF' , a temporary rise at R , after which it remains permanently lowered until the air enters the case as shown at P ; at that point the blood pressure curve also goes up, as is seen at HH' .

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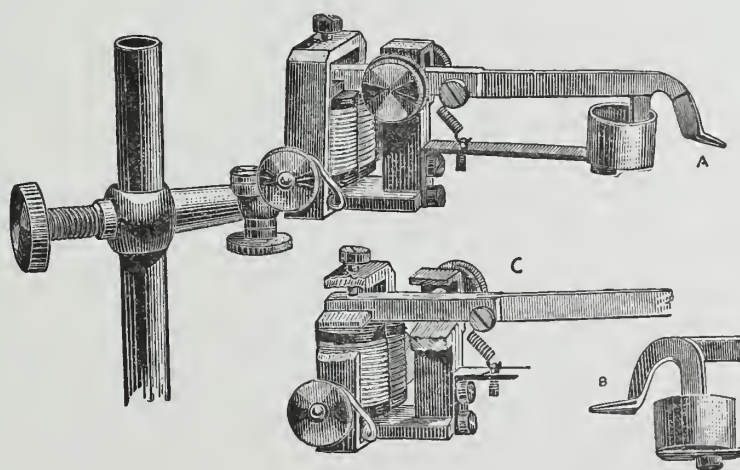


XVI.

A SELF-FEEDING CHRONOGRAPH PEN.

[*Studies from the Biological Laboratory of the Johns Hopkins University,*
Vol. II, 1880.]

The little instrument here described presents no novelty of idea, but has proved so handy and useful in the laboratory of the Johns Hopkins University, that I have thought well to describe it for the benefit of others. The idea was suggested to me by a similar instrument used by my colleague Prof. Rowland in the physical laboratory for writing on a horizontal surface, which, with a little trouble, I succeeded in modifying so as to fit it to write on the vertical paper of Ludwig's kymographion. Whoever has worked much with that instrument has probably been frequently annoyed by having his chronograph or stimulation pen give out at some critical moment, since the glass pens commonly used do not hold enough ink to last throughout a prolonged experiment. Moreover, when the instrument is not running, they are very apt to trickle down the paper. The self-feeding pen, once charged, will last for hours without fail and does not trickle.



The instrument is represented, three-fourths its actual size, in the woodcut A. Its essential part consists of a brass lamina curved in a vertical plane for most of its extent, and having a deep but narrow groove cut in its convex edge. One end dips into the little brass cup,

represented along with the brass lamina alone at B; this, when the pen is in use, is filled with the ordinary kymograph ink. The other end tapers off to a bluntly rounded writing point, and the pen is bent so that this part lies at right angles to the rest and in a horizontal plane. In the horizontal portion the groove is carried through so as to form a complete slit with a "nib" above and below it. If the other end of the pen be dipped in the brass cup, the writing point will not always be charged by capillarity, but if the groove be once filled by dropping a little ink from a fine pipette into its highest part, and this ink be spread out if necessary between the nibs, by passing a strip of paper between them, the pen will thenceforth keep itself filled from the reservoir, so long as there is any ink in the latter.

The accessory parts of the instrument are easily understood from the figures and may, of course, be greatly modified according to the end in view in different cases. The pen proper, in the form I find most convenient, is carried on the long arm of a lever, which is depressed by a little brass spring. The short arm of the lever carries a soft iron armature which is attracted by an electro-magnet whenever the circuit in the latter is closed, whether by a seconds clock or otherwise. The pen point is thus raised and remains so until the circuit is broken, when the spring above mentioned again depresses it. The screw shown above the armature regulates the amount of these excursions; it should in all cases be so fixed that the end of the pen does not strike against the bottom of the reservoir; otherwise the ink in the latter splashes. The whole instrument is carried on a short horizontal arm movable up and down a vertical support. Where the carrying arm joins the instrument proper is a joint permitting free motion in a horizontal plane. The vertical rod being in addition movable, by means of a slot in the plate which carries it, in any horizontal direction for more than two inches, the position of the writing point is easily adjusted. It should be arranged so that the axis of the horizontal part of the instrument is nearly perpendicular to the paper, and so that only the exact tip of the writing point touches. That half of the lever next the pen, being made of thin brass, acts as a spring by which the pressure of the pen point on the paper can be regulated.

I commonly now use two such pens with the kymograph; one for the "time," the other for the "stimulation" record. They are both carried on the same vertical rod, and the upper one is modified so that its electro-magnet is above the lever instead of below it. The lower instrument can

then be brought close up, so that the writing points of the two come within an inch of one another on the same vertical line. By slight modifications, removing the upper reservoir out of the way of the lower pen, the two could readily be brought still closer together if desirable; but as my kymographs are Fulcher's new ones with an eight inch wide roll of paper I have never been cramped for room.*

*The instrument may be obtained from T. Schneider, Mechanician, Johns Hopkins University, Baltimore, U. S. A., or from R. Fulcher, Panton Street, Cambridge, England.

XVII.

THE STUDY AND TEACHING OF BIOLOGY.

AN INTRODUCTORY LECTURE DELIVERED AT THE JOHNS HOPKINS
UNIVERSITY, OCTOBER 23, 1876.

[*Popular Science Monthly*, Vol. X, January, 1877.]

We meet to-morrow to formally begin the biological work of this University—to commence that systematic study of animal and vegetable form and function, relationship and distribution, which we include under the names of Comparative Anatomy, Zoölogy, Physiology and Botany, or in the general terms Biology or Natural History. I have thought that it might be well to-day to take an opportunity of laying before you what seem to be the ends which we should hold in view, and the methods on which we should work, if we are to attain or to deserve a permanent success. I am further induced to take this course by the fact that our present year's work is confessedly of a tentative nature: one main object of it being to enable us to decide upon what lines we are to go forward in the future; and I believe it may facilitate decision on some points if we have before us, as a sort of basis for discussion, a definite statement of views on the subject, no matter how imperfect such statement may be in itself, or how much the opinions expressed in it may afterward be found to require modification. What I propose, therefore, is not simply to tell you what are our arrangements for this year, but also to put before you some thoughts as to what I think we ought to do in the time to come. It is, I am sure, unnecessary for me to dilate at any length, before this audience, upon the interest and importance of biological studies. However contributory to our culture and welfare other studies may be, biology has, and ever must have, a very special interest of its own: it alone deals with the living organisms which surround us, and which are the only things that share with us that wonderful collocation and interaction of natural forces which we call *life*. Biology, too, includes within its range the study of man himself, so far as one side of his nature is concerned; and, as regards his mental and moral qualities, the psychologist and sociologist have already begun to recognize that the progress of their

sciences is closely bound up with the development of certain branches of biology. As regards its practical value I might set forth at length the indebtedness of scientific medicine and of sanitary science to biology ; but I prefer not to recommend the study to you by such considerations. This is a university : and the object of a university, I take it, is directly to promote liberality of thought and culture, and only indirectly to concern itself with the practical advancement of material welfare. It is concerned rather with the acquirement of a knowledge of principles than with their practical applications : although, in connection with it, it may have subsidiary schools where those who have already learned the principles may acquire a practical knowledge of various arts. Nevertheless it is true that, if we devote ourselves to the higher objects, the rest will be added unto us ; for it is one of the great glories of all the physical sciences that, while second to none in the training which a study of them gives to all the faculties of the mind—in the promotion of large and liberal ideas, and in the gratification of that longing to “know,” which is the noblest characteristic of the human intellect—they at the same time, as a by-thing, but constantly, contribute to the increase of man’s comfort, and to the material prosperity and happiness of his race. Those who advance our knowledge of the laws of animal and vegetable life may work without any immediate outlook to the advancement of medicine, hygiene and agriculture, but such advancement constantly follows and springs from their work, and will ever do so.

To those who are in any degree acquainted with the state of the scientific world, the present must seem a specially opportune time for founding a biological school. At no previous period has such an interest been taken in biological problems, or have so many earnest workers been in the field—never before has so rich a harvest been in view. This is mainly owing to the promulgation of two great ideas within the last few years. On the morphological side we have the doctrine of evolution applied to living forms, and especially as definitely put forward by the theory of the origin of species by natural selection ; while on the physiological side we have the doctrine of the conservation of energy, and its extension to the play of forces in living organisms. It matters not whether these theories be correct representations of the facts or not, or whether increase of knowledge confirms or upsets them—in any case they have been of incalculable importance in stimulating work and in giving a present and direct significance to its results. I can imagine no time for the biologist to live in which would be more interesting than the coming

half-century, or none in which he will have a greater incentive to study ; he seems to have almost within his grasp the solution of problems of the widest significance.

Those of us directly concerned in the administration of the biological laboratory here, are charged with the fulfillment of two duties : we have to make provision for the advancement of knowledge, and for its diffusion ; we are to find accommodation and assistance for both investigators and students ; while we must not suffer those engaged in research to be crowded out by beginners, neither must the beginners be overlooked in providing for those to whom they are one day to succeed. The liberal space at our disposal will permit us, at any rate for the present, to accommodate both classes of workers, without risk of the extermination of either. Meanwhile I have, then, to occupy your time with a few words on two subjects : on biological research, and on biological teaching.

One hears a good deal talked nowadays of scientific research, and among it a good deal of what I cannot but think mischievous nonsense about the peculiar powers required by scientific investigators. To listen to many, one would suppose that the faculty of adding anything whatever to natural knowledge was one possessed by extremely few persons. I believe, on the contrary, that any man possessed of average ability and somewhat more than average perseverance, is capable, if he will, of doing good original scientific work. Any hard-working and commonly intelligent man, who likes his profession, will make a good soldier, or lawyer, or doctor, though that combination of powers which makes the great general, or the great jurist, or the great physician, is given to but few.

So it is with the pursuit of Science : assuredly not every one of her followers, very probably not one among us now present, will become a Linnæus, or a Cuvier, or an Agassiz. It may not be given to any of us to make some brilliant discovery, or to first expound some illuminating generalization ; but we can, each and all, if we will, do good and valuable work in elucidating the details of various branches of knowledge. All that is needed for such work, besides some leisure, intelligence and common-sense (and the more of each the better), is undaunted perseverance and absolute truthfulness ; a perseverance unabated by failure after failure, and a truthfulness incapable of the least perversion (either by way of omission or commission) in the description of an observation or of an experiment, or of the least reluctance to acknowledge an error once it is found to have been made. Moreover, this love of truth must extend

to a constant searching and inquisition of the mind, with the perpetual endeavor to keep inferences from observation or experiment unbiased, so far as may be, by natural predilections or favorite theories. Perfect success in such an endeavor is, perhaps, unattainable, but the scientific worker must ever strive after it; theories are necessary to guide and systematize his work, and to lead to its prosecution in new directions, but they must be servants, and not masters. I may, perhaps, seem to be insisting at too great length on a self-evident point; but the more one knows of scientific work and workers, the more does one realize the importance and the difficulty of attaining a perfectly balanced mind and of arriving at an unprejudiced deduction from observation.

I believe, then, that the only absolutely necessary faculties for the scientific investigator are love of his work, perseverance, and truthfulness; to make the great leader and master in science, one of those who cast a new ray of light on our conceptions of the universe, other and far rarer powers are, of course, needed—the most essential being originality of thought; and, as that cannot be either self-taught or taught from outside but must be born in the bone, all that the rest of us can do when we meet such men is to give them a free course and ungrudging help. That an army may attain its best success, needs indeed that every man be brave and loyal, but it is by no means requisite that every soldier be a brigadier-general; so in the army of Science, there is place for soldiers of all ranks and capabilities—and, at any rate, we know this, that Nature reveals her secrets, which are her rewards, on no system of purchase or favoritism—what a man deserves that he gets, every drummer-boy who enters her service carries the marshal's *bâton* in his pocket. His reward will be proportionate to the amount of time and intelligence he devotes to his work; given, in addition, certain opportunities which every one has not for himself, but which it is one great object of such institutions as this to provide for all.

If what I have just stated be the general requisites of the scientific investigator, we have next to inquire what special needs has the biologist: these may all be grouped under the head of preliminary training. He must have a fair knowledge of mechanics, experimental physics, and chemistry; he ought to (I would almost again say he *must*) be able, besides English, to read at least French and German with facility—assuredly, if he cannot, he will labor with much toil and sorrow—and the more mathematics he knows, with the present rapid importation of quantitative ideas into biological science, the better for him; and for certain special

branches of biological work there are other special needs. No mistake is more disastrous than the idea that a man can be a botanist and nothing more; a zoölogist, and nothing more; a physiologist, and nothing more. It is true that no one can be master of all the physical sciences, but it is none the less true that hardly one of them can be entirely neglected by the biologist. Animals and plants are, after all, material objects, and live in accordance with the laws that govern matter; but the manifestations of these laws are so often obscured and complicated by the conditions in which they occur in living things, that the understanding of them is only to be got at by approaching them through their simpler manifestations in inorganic bodies. But, apart from that, definite knowledge of various sciences is constantly required by the biologist. How can one ignorant of physics have any real appreciation of the statement that the transmission of a nervous impulse is accompanied by a molecular alteration in the structure of a nerve-fibre, one sign of which is a certain very definite and peculiar alteration in its electrical properties; or how can one ignorant of chemistry grasp the fundamental statement that muscular work is in the long run dependent on the breaking down of complex chemical molecules into simpler and more stable ones? How can the zoölogist or botanist scientifically study the distribution of animals and plants in space, unless he has a knowledge of physical geography; or in time, unless he knows something of geology? I need not prolong the list.

Furthermore, no one can properly study any branch of biology without some knowledge of its other divisions. The fundamental laws of animal and vegetable life are identical, and only fully realized by comparison; so, while the scientific botanist, to fully appreciate the facts of his own science, must be something of a zoölogist, so must the zoölogist know something of plants: no one living being or group of living beings can be properly understood by itself. To take other examples: how is the morphologist to deal with such problems as those presented to him by rudimentary organs, unless he know something of the functions of parts, which is the special domain of physiology; or, how is he to understand the influence of external conditions in the production and preservation of variations in force, without, again, this knowledge of function? And, as regards the physiologist, he has frequently to search the whole animal and vegetable kingdoms not only to discover those forms which give him the best opportunity of studying certain phenomena, but also to get at those fundamental ideas which lie at the base of

his whole science. What general and broad ideas should we have of the contractility of protoplasm if we only knew it in the highly-specialized form of a muscular contraction ; or of its irritability, if we only knew it as exhibited in the nervous apparatus of one of the higher animals? It is quite true that, without any breadth of knowledge, a man may collect, label and store away thousands of plants ; he may macerate and articulate the most beautiful skeletons ; he may cut, stain and mount, the most exquisite microscopic preparations : but assuredly he is not likely to do any work entitled to the name scientific ; such mechanical work has its value, no doubt, but it is only preliminary to real scientific work—which latter requires wide knowledge and extended views, and is more valuable the broader the foundation on which it has been built up.

It is this mutual dependence of biological studies which appears to me the justification of grouping together, as we do here, the study of such a number of vast subjects in a single laboratory. By that means each investigator will receive knowledge and assistance from the other ; under such a system the desirable intercommunication of ideas is rendered most easy ; and we are most likely to escape that narrow specialism which every laboratory in the long run has a tendency to get into. Of course, no one person is capable of giving detailed assistance in investigations in all the branches of biology ; but our staff of professors will doubtless grow, and meantime we shall, I trust, by the associate and fellowship system of the university, have at all times among us well-qualified men in every branch of biology ; so that no one fitted for the task, and earnest and willing in its prosecution, who may come here to undertake any special research, will fail to find some one able and willing to advise him when he needs advice, and to assist him when he needs assistance.

What we want here, then, is men with the requisite zeal and training for investigation—we care not whether classification, or morphology, or physiology, or any other branch of biology is their specialty ; all we claim is that they shall be able to work, shall mean to work, and shall work—we shall give no quarter to the indolent or ignorant : the former we will not have on any terms, and the latter must enter for the preparatory courses, and will not be allowed to occupy tables set apart for research. Surely, if we select wisely, and find men to work faithfully, we may look forward with confidence to the time when we shall find ourselves in the condition of such laboratories as those of some of the German universities, where, on account of the high class of work done in them, the ablest young men from all over the world beg for admission ;

where one finds, working side by side, men from every civilized nation, and where, in the presence of the great demand for admission, entry is esteemed a precious privilege.

As to the special aid which we can offer to those who come among us to engage in investigation, it will, of course, depend on two factors, upon the natural gifts of those charged with the supervision of the laboratory, and the amount of money which those whose duty it is to decide on such matters see right to place at their disposal; for, however important we biologists may think ourselves, the fact remains that there are other studies to be provided for, and studies just as important as our own. For the present I can say, however, that we have at our disposal one large and well-lighted room for general work—a room fitted up for physiologico-chemical investigations—and several smaller rooms for physiological and histological research. As regards instruments we have ordered, and in part received, a very excellent stock, including the most essential ones for every branch of physiological research—and I have no doubt that every year we shall receive grants to add to our stock, and keep up with the times.

The zoölogical and comparative anatomy departments differ from the physiological in not needing so many special instruments; what they mainly need are (besides work-rooms) material for examination and dissection, and books, especially monographs, and those we shall make it a point, to the best of our power, to obtain from time to time as they are wanted. It seems to me that it is not our duty to provide vast herbaria and museums containing every plant and animal under the sun—to provide such collections is the duty rather of the nation than of a university—nor do I think we should be wise to collect and store away things promiscuously in the hope that some one will want them some time. We should rather concentrate our force on getting what is wanted for the time being. If some one wants to elucidate any point in the structure of the Echinoderms, for example, we should do our best to obtain specimens for him—even from all parts of the world; if some one else wants to work at the embryology of any fish or amphibian, we should again endeavor to get him the eggs in various stages of development, and so on; but I doubt the wisdom of sending out collectors with orders to store away everything they can catch, fish, flesh and fowl, in spirit, and send it to us. We have nowhere to display such collections if we got them—the vastly greater part of them would never be used—and when reference to extensive collections is necessary, we have always at

hand the admirable museum illustrating the fauna and flora of this State which is being brought together by the Academy of Sciences in this city, and the national collections at Washington are within an hour's journey of us. Bringing together from time to time such materials for special researches as I have indicated above, will naturally entail considerable expenditure, but I am sure that the trustees, if they see we mean work, will do all they can to supply our needs.

Now let us turn to the other part of our subject, biological teaching: from part of what I have already said you have doubtless gathered something of my views on this matter. If biology be the complicated study that I have endeavored to indicate, it is in the first place clear that, in justice both to the student and his teachers, a certain preliminary training must be insisted upon as a preparation for his admission to a biological laboratory; at least the student must have a fair knowledge of physics and chemistry before he comes there; and, when he gets there, the thing next to insist upon is that his teaching be as largely demonstrative and practical as possible, lectures being made of secondary and laboratory work of primary importance.

It matters not to me where the student gets this preparatory knowledge; whether here or at some other institution. I believe he ought to acquire it largely at school, as a part of general education; but as that seems in the present condition of primary education almost impossible, I shall perhaps best make clear my ideas on the matter if I endeavor to sketch out what I think should be the course gone through by a youth fresh from some high-school or college, where he has got an otherwise sound general education, but without anything more than a sham knowledge of physics, and who enters this university with the intention of qualifying himself for biological research or teaching hereafter; and you will, I hope, forgive me if, with the same object of obtaining clearness, I put what I have to say into a somewhat dogmatic form.

Such a person ought to enter at once upon courses of instruction in experimental physics and chemistry, and devote almost wholly his first year to them; but during the latter part of that year, say between the spring vacation and the end of the session, he would, in addition, go through a course of instruction in what we may call general biology. By that I mean a course of instruction in which he would acquire some knowledge of how to use his microscope and how to dissect, and thus gain a certain amount of that special manipulative dexterity which he will require afterward. He would also gain a general acquaintance with biolo-

gical ideas, and with the meaning of the more important technical terms; he would gain, for example, a real, because a practical, knowledge of what we mean by classification, and of the principles on which classifications are founded; he would learn similarly, with his eyes as well as his ears, what we mean by morphology, and homology, and a host of similar terms; and he would, in addition, acquire a special acquaintance with the structure and actions of certain selected typical animal and vegetable forms. This, then, would finish the first year's work, unless our student should be ignorant of French and German. If so, he ought also to acquire, what is really very easily got, at least a fair reading knowledge of those languages.

At the commencement of his second year the student should enter for two elementary practical courses, one on comparative anatomy and zoölogy, the other on animal physiology. These courses would, I imagine, last about six months each, and they should be taken *pari passu*. Each would consist, say, of two lectures a week, and the rest of the time would be filled up with the dissection of typical animals, the performance of the simpler physiological experiments, and the preparation and examination of microscopic specimens of animal tissues, all illustrative of the main points put forward in the lectures. The student would also be made to draw sketches of his dissections and microscopic preparations, and to describe them and the results of his experiments briefly in writing, and so while learning thoroughly how to dissect and use his microscope, and the conditions of success in physiological experiment, he would also have his powers of observation regularly trained and tested.

In connection with these courses there should be a museum, containing not a bewildering multitude of specimens, but a small number of dissections and skeletons of typical animals, especially of those which it is important for the student to know, but which are too rare to be obtained in quantities allowing each to dissect one for himself; and these specimens should be so placed that they may be freely accessible to those desiring to study them. It is far better to have to replace an injured specimen occasionally, than to have the things locked up behind glass doors, so as to render their thorough examination impracticable to those for whose examination they are placed there. Moreover, especially in connection with the physiological course, there would be needed from time to time, according to the subject-matter of the lectures, demonstrations of certain points; in cases, for instance, needing the employment of the more delicate instruments, or where niceties of manipulation were required, such as a beginner could not be fairly expected to overcome.

I ought perhaps here to refer to the subject of vivisection. Physiology is concerned with the phenomena going on in living things, and vital processes cannot be observed in dead bodies; and from what I have said you will have gathered that I intend to employ vivisections in teaching. I want, however, to say, once for all, that here, for teaching purposes, no painful experiment will be performed. Fortunately, the vast majority of physiological experiments can nowadays be performed without the infliction of pain, either by the administration of some of the many anæsthetics known, or by previous removal of parts of the central nervous system; and such experiments alone will be used here for teaching. With regard to physiological research the case is different: happily here too the number of necessarily painful experiments is very small indeed; but in any case where the furtherance of physiological knowledge is at stake—where the progress of that science is concerned, on which all medicine is based, so far as it is not a mere empiricism—I cannot doubt that we have a right to inflict suffering upon the lower animals, always provided that it be reduced to the minimum possible, and that none but competent persons be allowed to undertake such experiments. Placed, moreover, as we shall be here, in more or less close connection with a splendidly-equipped hospital, so that we shall be able constantly to combine skilled pathological observation with physiological experiment in an excellent laboratory, we have duties to perform toward the advancement of scientific medicine, from whose performance I believe it would be criminal in us, as it would be shameful, to flinch in any way.

But to return to our special subject: the last three months of the student's second year should be occupied with a laboratory course of instruction in vegetable morphology and physiology, and with a course of lectures on embryology, accompanied with a full practical study of the development of the chick from the earliest stages of incubation.

The student will have now got an extensive acquaintance with biological facts and methods, and henceforth he should be allowed and encouraged to specialize his work. He would be permitted to select for more detailed study in his third year either animal morphology, or botany, or physiology, and the best men in each subject would be picked out and allowed to act as demonstrators to the second-year students, and so be given the opportunity of acquiring a far more accurate knowledge than they could attain in any other way. For these third-year men, too, short advanced courses of lectures would be given from time to time, such as on the physiology of nutrition, the physiology of the senses, the

geographical distribution of animals, on special morphological points, and so on, and also on the more important recent discoveries in various branches; and the best of them might be put on some easy bit of original work, to try their metal and whet their appetites.

After all this has been gone through, I think we can do no more in the way of teaching for our typical student; he has now advanced enough to teach himself, and, if he is good for anything, will do it better than others can do it for him. I think that among students so taught, as I have endeavored to indicate, we should be certain to meet with a large number of well-qualified men from among whom to select some of our fellows and associates, and would be justified in expecting from them work of the highest quality. As regards the remainder, those who display no special aptitude for scientific investigation, or no desire to devote themselves to science as a profession, they will at least have had the opportunity of acquiring a very thorough and practical knowledge of what modern biology means.

It now remains for me to give a sketch of what our work for the present year will be, so far as I see my way at present. To-morrow I commence a course of lectures on animal physiology, which I propose to deliver twice a week, on Tuesdays and Fridays at 1.15 p. m. I have been induced to select this hour on account of special circumstances affecting many of those who wish to attend this year, though as a general rule I should like an earlier hour, nine or ten in the morning, which definitely brings a man early in the day to the laboratory, and gives me a better chance of getting a good day's work out of him. These lectures will be designed rather for those who have already some knowledge of physiology than for beginners; for so many instruments have not yet arrived, and so many arrangements are necessarily as yet imperfect, that it seems better for the present only to invite men who are more or less fitted by previous training to overcome such occasional difficulties and inconveniences as may from time to time arise from such causes. When I say that the lectures will be rather adapted for advanced students than beginners, I do not mean, however, that I shall omit elementary but important facts, but that, in addition to those, I shall from time to time discuss at more or less length points which are still *sub judice*. The lectures will be illustrated by no experiments: partly because on account of the rapid changes which go on in living tissues, physiological-lecture experiments are likely to be the reverse of successful (a frog's muscle which has been lying on the table since the commence-

ment of a lecture is very apt to contract abnormally when the lecturer wants it), but mainly because I want each student to make the illustrative observations and experiments for himself—except in cases of unusual difficulty, when demonstrations will be given at such hours as may be found most convenient to the majority. In the lectures I shall presuppose the possession by each present of such a knowledge of anatomy as is necessary for physiological work, and, starting with the structure of blood, go regularly on through the histology and physiology of the tissues and organs of the animal body. These lectures will continue until the spring vacation, and then I mean to set to work specially for more elementary students and put them through such a course of general biology as I have already described; but possibly either Dr. Brooks or myself will give at that time some instruction in embryology of a more advanced character.

As regards physiological research, several gentlemen have already consulted me with reference to undertaking investigations in different directions, and of course there is plenty of work to be done should others qualified for it present themselves. One difficulty which I have met with is that many seem to consider that a physiological investigation can be carried on by devoting to it an hour or two at irregular intervals; I feel quite sure that no good work is likely to be done in that way, and am not inclined to encourage such workers. Some, at least, of those engaged in investigation will be able to have accommodation in the special rooms, apart from the general laboratory, which have been provided for that purpose.

On the zoölogical and morphological side no arrangements have as yet been made for a lecture and laboratory course this year, nor so far as I know has any such demand as would render it advisable shown itself. Should it do so, however, we may perhaps make arrangements for elementary instruction in those subjects, under the more immediate superintendence of Dr. Brooks, our associate in biology, upon whose shoulders I must throw most of the burden of that side of the work. We shall, at any rate, collect material and make other preparations for such a course next year. After Christmas Dr. Brooks will give a course of lectures on "Morphological Theories."

For the present, too, we shall have in the laboratory several well-trained zoölogists and morphologists; some engaged in prosecuting advanced studies, others in research. I fancy all of them are (as they ought to be) pretty well qualified to take care of themselves; but Dr.

Brooks and myself will do our best to give them such assistance as they may need, and to make arrangements by which they can be supplied with such material as they require.

In conclusion, let me say a word to those of you here present who are to be the first workers with me in this laboratory. It behooves you as well as me to recognize what a heavy responsibility lies upon us. Upon the work that we do and the spirit in which we do it, upon the character we give our laboratory at its start, much of its future success or failure depends. If we all work honestly and thoroughly, it will win esteem and reputation; if we are careless and half-hearted, it will become of low repute. Let us, then, each work loyally, earnestly, truthfully, so that when the time comes, as it will come sooner or later, in one way or another, to each of us, to depart hence, we may carry with us a good conscience, and be able to say that in our time no slipshod piece of work ever left the laboratory; that no error we knew of was persisted in; that our only desire was to know the truth. Let us leave a record which, if it perchance contain the history of no great feat in the memory of which our successors will glory, will at least contain not one jot or one tittle of which they can be ashamed.

XVIII.

THE PHYSIOLOGY OF SECRETION.

ANNUAL ADDRESS DELIVERED BEFORE THE MEDICAL AND CHIRURGICAL
FACULTY OF MARYLAND, APRIL 9, 1879.

[*Transactions of the Medical and Chirurgical Faculty of Maryland, 1879.*]

When your Executive Committee did me the honor of asking me to address you to-day my first impulse was to decline the responsibility. Not indeed from any want of good-will to your organization, but because I have always some sort of shame in meeting a number of medical men, collected together as such ; being myself one who has put his hand to the plough and not only looked back but gone back from the laborious course of the physician or surgeon, into what seemed the more pleasant by-paths which tempted me on the road. As a consequence of this I am but little acquainted with the problems which are of prominent interest to you at this moment ; ignorant to a great extent of what they are, and still more of any details concerning them, and so am but little fitted to take the place of the distinguished member of your profession whose untimely death has prevented his standing to-day in the position towards you which I now occupy.

Still I have never lost entirely my early love, nor ceased to regard the practice of medicine as among the noblest of all the pursuits in which men are engaged ; and am always fain to look upon myself as a sort of camp-follower in your army, who, though not destined himself to bear the brunt of the fight with disease and all its attendant human miseries, yet is glad to believe that he may be so fortunate as to succor at times those who fight in the outposts.

Looking around the field of combat, it seemed possible that a discussion of some one of the newer problems of physiology might be of interest to you ; since the toilsome life of the medical man leaves him but little time to learn more of the advances of that science than such brief abstracts as are found in the medical periodicals. Of all the current subjects of physiological inquiry it seemed that there were at present none of greater importance than those relating to the physiology of secretion ; a subject which I might hope would have a special interest to

you, as being calculated to throw light not only on cell life in general, but as serving well to bring into prominence the relative influence of the nervous and vascular systems upon the mode of life of the various tissues of the body, and so having some importance with reference to pathological problems.

With your permission I propose to occupy a few minutes with a sketch of some common phenomena of cell life, before proceeding to secreting cells in particular. Not that I suppose the fundamental points to which I am about to refer are unknown to you; but as I wish to look at the mode of life of a gland cell in relation to the modes of life of animal cells in general, it will be advantageous to have the main facts with respect to the latter fresh in mind.

Among the simplest elements entering into the composition of the human body are such cells as the lymph or pale blood corpuscles; minute granular protoplasmic nucleated masses, with no definite cell wall. Each of these simple bodies exhibits of itself certain properties which are distinctive of all living things as compared with inanimate objects.

In the first place it can take up new materials from the outside and build them up into its own peculiar living substance, the new material not being deposited (at least necessarily or always) on the surface of the cell, but laid down in its mass between the already existing molecules. Moreover, the chemical bodies received from outside are either uncombined elements, as oxygen, or elements combined in a different manner from that in which they exist in the living protoplasm. They only become part and parcel of the cell, "flesh of its flesh," after it has wrought chemical changes in them.

By this reception from the exterior the cell grows, but the increase of size which may be brought about in that manner is not indefinite, being limited in two ways. Alongside of the reception and deposit of new material there occurs always in the living cell a breaking down and removal of the old; and when this disintegration equals the accumulation of new material, as it does in all the cells of the body when they have attained a certain size, *growth* of course ceases. The disintegration is due to the chemical metamorphoses by which energy is liberated for the performance of such work in the cell as is necessary for its vital maintenance; and as the necessary work increases disproportionately fast, growing with increase of bulk as the cube of the diameter, while the receptive powers, primarily dependent on the area of the surface of the cell, increase only as the square, at last a size is attained at which

chemical degradation and elimination equal the reception and chemical construction going on in the cell, and growth ceases.

The second limitation to indefinite growth is connected with the power of the cell in one way or another to give rise to new cells like itself. Under certain circumstances, as yet imperfectly known, the pale blood corpuscle becomes narrowed at one zone; the constriction deepens until the parts on each side of it are merely connected by a slender band, which finally gives way and two independent cells are formed. Commonly the nucleus divides before the rest of the cell, and so the result of the process is a pair of cells, each like the original one but for their smaller size. These grow as the mother cell did and may in turn multiply in the same manner.

These two faculties, that of taking in and working up into their own substance materials derived from outside, or *assimilation*, and that of in some way giving rise to new beings like themselves, or *reproduction*, are possessed by all living beings whether animals or plants. There is however an important difference between them; assimilation is necessary for the maintenance of each individual cell, plant or animal, in order to replace its never-ceasing wastes, but the power of reproduction is necessary only for the maintenance of the kind or race, and need be and often is possessed only by some of the individuals composing it. Working bees for example cannot reproduce their kind, that duty being left to the queen-bee and drones of each hive.

The breaking down of already existing chemical compounds into simpler ones is as invariable in living things as that building up of new complex molecules referred to above. Reception, chemical construction, chemical degradation and removal of the products of the latter, form a series of correlated phenomena of cell life which we sum up under the name of *nutrition*. From this series of nutritional phenomena, however, we may conveniently separate those implying chemical changes under the name of *metabolism*, and it is this part of cell life that has the more immediate interest for us in connection with the present subject.

In addition to the phenomena of nutrition, the pale blood corpuscles present certain other phenomena which, though not so absolutely diagnostic, are yet very characteristic of living things.

Examined carefully with the microscope on a warm stage, they exhibit the well known amoeboid movements. They undergo changes of form independent of any pressure which might distort or otherwise mechanically alter their shape. The faculty of the cell upon which these

form changes depend is known as *contractility*, a word which in a physiological connection is of course something quite different from the contractility of a stretched india-rubber band, which tends merely to reassume a form from which it has previously been forcibly removed.

Another important property of such cells is their *irritability*. An amœba coming into contact with a solid particle calculated to serve it as food, will throw out around it processes of its substance and gradually convey the foreign mass into its own body, the amount of energy expended by the animal in so doing being altogether disproportionate to the force of the external contact. The foreign particle does not actively push-in the surface of the amœba and burrow into it, but the mere touch arouses in the amœba an activity quite incommensurable with the exciting force, and comparable to that liberated by a spark falling upon gunpowder, or by a slight tap upon a piece of gun-cotton. It is this disproportion between the excitant (or *stimulus*) and the result which is the essential characteristic of physiological irritability. In this regard observation shows that pale blood corpuscles may behave exactly like amœbæ, taking up into their own substance in a precisely similar way minute solid particles injected into a vein. In this way, as in others, for example their contraction into rigid spheres under the stimuli of electrical shocks, they show that they too are endowed with irritability.

Further, when an amœba or one of these pale corpuscles, coming into contact with a foreign object, proceeds to draw it into its own substance, the activity aroused is not merely displayed by the parts actually touched. Distant parts of the cell also coöperate, the influence of the stimulus is not local alone, but as a result of it a change is brought about in remote parts of the cell. In other words, the cell substance is physiologically *conductive*.

Finally, the movements exerted are not random, but are adapted to attain an end. They are so combined as to bring the external mass into the interior of the cell. This faculty of all the parts to work together in definite strength and sequence to attain a particular result, is what we know as *coördination*.

These four powers, or faculties, irritability, conductivity, contractility, and coördination, which, with nutrition and reproduction, we may call the fundamental physiological properties, are also possessed in a high degree by our bodies as a whole. To take a trite but excellent example, having which to hand it is not worth while to seek further, we all know

that if the interior of the nose be tickled by a feather a sneeze usually results. The feather-touch or "stimulus" calls forth movements which are mechanically altogether disproportionate to the energy spent in the contact. The body is then highly *irritable*. The resulting movements, themselves a manifestation of *contractility*, are not exhibited at the point touched, but at more or less distant parts in abdomen, chest and face, so our bodies are physiologically *conductive*; and finally the movements resulting are not random convulsions, but are so combined as to produce a current of air through the nose calculated to remove the irritating object. In this we have a manifestation of *coördination*.

Speaking broadly, these four properties are more obvious in animals than in plants, but they are by no means confined to the former. In the sensitive plants, touching one leaflet will excite regular movements of the whole leaf, and similar phenomena are exhibited by the Venus's fly-trap and other plants.

On the other hand no one of these properties is characteristic of living things in the way that their mode of growth (by intussusception) and power of reproduction are. Irritability is but a name for unstable equilibrium and is as manifest in nitro-glycerine as in an amœba or a muscle; in a telephone the influence of the voice is conducted as a molecular change along a wire and produces results at a distance, and innumerable inanimate machines afford examples of the coördination of movements to attain a definite end.

There is however another phenomenon presented by many living cells in which they appear at first to differ fundamentally from not-living objects. This is their apparent *spontaneity* or automatic power. Lymph corpuscles frequently change their form independently of any observed external cause or stimulus; while a dead mass at rest, and unacted upon from outside, remains at rest. Closer examination, however, leads to the conviction that this difference is only superficial; it depends in fact, not upon a peculiar spontaneity of the living cell, but upon its nutritive powers. Any system of material particles in equilibrium and at rest will forever remain so if unacted upon by any external force. Under certain conditions such a system can carry out a series of changes when once a start has been given; but it cannot initiate them itself. Every living cell being in the long run a complex system of molecules, composed in their turn of chemical elements, if we suppose the whole set of atoms in equilibrium at any moment, no change can be started in the cell from inside; in other words, it will have no real spontaneity. When, however, we take

into account the irritability of amœboid cells, or in other words their unstable molecular structure, it is clear that a very slight external agency, such as may completely elude our present methods of observation, may set going in them a great series of changes, just as a slight shake will upset a card house.

Once the equilibrium of the molecules has been disturbed, movements of some or of all will continue until the atoms constituting the cell have again settled down into a stable state. But in living cells the re-attainment of this state may be, and frequently is, indefinitely postponed by the reception of new substances, food in one form or another, from outside, and by the metabolic powers of the cells. The nearest approach to a complete equilibrium in living matter is probably exhibited by the resting state into which some of the lower animals, as the wheel animalcules, pass when dried slowly at a low temperature. The removal of water checks their metabolism, that is to say those nutritive processes by which the attainment of molecular equilibrium would otherwise have been prevented.

If therefore we employ the terms "spontaneity" or "automaticity" to signify a power in a resting system of particles of initiating changes in itself, then they are applicable to neither living nor not-living things. But if we simply use the word "automatic" to designate changes the starting cause of which we do not recognize, and which in many cases acted long antecedently to the changes which we *do* see, then the term is unobjectionable and convenient; as it serves to express briefly a phenomenon presented by many living cells; but it then designates no longer a property peculiar to them. A steam engine with its furnace lighted and water in its boiler may be set in motion by opening a valve, and the movements then started will continue automatically in the above sense until the coals or water is used up. The essential difference between it and the living cell is to be sought in the nutritive powers of the latter which enable it to replace continually what answers to the coals and water of the engine.

Now, as you all know, at a very early stage of its development the body of each of the higher animals consists solely of an aggregation of such nucleated cells as those which we have been considering. I mean when it exists as the mulberry mass or *morula*. At that time the constituent units of the body are all alike; no different tissues, and still less any organs, being recognizable.

For some time the cells of the morula simply multiply by division, but soon new processes appear which ultimately give rise to the adult body with its many tissues and organs. Groups of cells ceasing to grow and multiply as their parents did, begin to grow in ways peculiar to themselves, and so they come to differ from the cells of the original morula and from the cells of other groups. By peculiar growth a varied whole is *developed* from a homogeneous one; as we say, the tissues are *differentiated*.

With the differences in structure appear differences in property, and then it becomes evident that the cell aggregate is not to give rise to a number of nearly independent living things, but to a single animal, in which each cell, while primarily looking after its own interests, shall have duties to perform for the good of the whole. A single compound individual is to be formed by the union and coöperation of a number of simple ones.

As differentiation goes on we find the fundamental physiological properties, originally possessed by all the cells of the morula, distributed between the modified cells which form the tissues, much in the same way as different employments are distributed in a civilized state. For the difference between the fully developed human body and the collection of amœboid cells which represented it in the morula stage, is essentially the same as that between a number of wandering savages and a civilized nation. As a nation is more advanced in civilization—has its necessary work carried on better and more economically—the greater the division of employments in it, so is an animal higher or lower in the scale according to the degree in which it exhibits a distribution of physiological duties between its tissues.

Ultimately in the human body we find specially irritable, specially contractile, specially receptive, specially metabolic, and specially eliminative tissues, united by supporting and connective tissues.

It is clear, however, that such a collection of living tissues would not make a man any more than a chance collection of a million persons would make a nation. In order that all shall coöperate and produce as the resultant of their individual lives one living animal, some bond of union is necessary; some arrangement of tissues by which the activities of all shall be subordinated to the welfare of the whole.

Primarily this bond is furnished by the nervous system, which, highly conductive, places the irritable tissues of the sense organs in connection with the coördinating nerve centres, and through these, with the

contractile, metabolic and certain other tissues; so that these may make changes responsive to the changes of external conditions which have stimulated the sense organs. To properly understand the activity of any tissue we must then know not only its special physiological property, but also its dependence, if any, upon the nervous system.

Secondly we find another great integrating bond in the blood and lymph. An animal composed of one or few cells, and so with a large surface in proportion to its bulk, may require no circulating liquid. Each cell can carry on its own changes directly with the environment, getting food from it in one form or another, and passing out its waste. But in a more complex organism consisting of millions of cells, and moreover, like man, living in the air, which necessitates a dense superficial covering to prevent excessive evaporation, the great majority of the tissues cannot be supplied directly from the surrounding medium. Between it and them must intervene something which shall convey excess of new materials from receptive cells in the lung or alimentary canal to others lying far from a free surface, and shall carry in turn the waste products of these to excretory cells, also in direct communication with the exterior.

This medium is afforded by the lymph primarily, which as it oozes through the serous canaliculi of the body is in contact with the tissues directly. But, more remotely, the blood forms the internal medium; in its circuit it takes up new materials from the richly charged lymph in the neighborhood of receptive cells; and wastes from the lymph in the neighborhood of working cells, to carry these latter products to the lymph about excretory cells. So that while the lymph is really the internal medium in which the cells directly live, yet the blood is a sort of resultant of all the interchanges between the tissues and the lymph, undergoing interchanges with the latter by dialysis and filtration in all parts of the body; so that it is practically correct, as well as convenient, to speak of it as the *internal medium*.

Through the circulating blood every cell may react upon every other cell. What each takes alters the blood, as well as what each gives, and so each cell may act upon distant parts; and the blood comes to form a second bond uniting all the cells into one living animal.

It is clear then that the mode of life of any cell in the body will or may depend upon three things: First, upon what we may call the physiological character or specialized property of the cell itself; secondly, upon its connections with the nervous system and the influence exerted by this upon it; and thirdly, upon the nutritive medium.

Disease, which is, fundamentally, abnormal tissue life, may depend on any of these factors; and at different periods one or the other has most engaged the attention of pathologists. The humorists looked mainly at the medium; the nervous school ascribed to the nervous tissues a great control on cell life; and then of late years, under Virchow's influence mainly, the cellular pathology brings the individuality of the cell itself into prominence in the production of disease. It is mainly as tending to throw light upon the influence of each of these factors on the physiological life of cells, and so upon their pathological, that I have selected secretion as the topic of this discourse.

As regards the medium, it is clear that any cause cutting off the blood supply, and preventing the arrival of food and the removal of waste from a cell, will lead to the alteration or cessation of its activity; an embolism will produce aphasia by preventing the renewal of the lymph around certain brain cells and fibres. On the other hand the absence of certain normal constituents of the blood or the presence in it of noxious bodies, may also influence the cells for evil, as in asphyxia and poisoning. But apart from this the question remains over, how far an abundant or excessive blood supply can affect the nutrition of cells, or their activity. Can you or can you not make a cell feed or work, simply by placing plenty of material within its reach?

Then as to nervous influences, which gained for some time a prominence, there is still much obscurity. The observation of cutaneous eruptions along the lines of certain nerves, and the ulceration of the cornea and parts of the buccal mucous membrane following section or injury of the trigeminal nerve, have been put forward as indicating a direct influence of the nervous system upon cell nutrition; but later work has in large measure weakened the potency of such arguments, brought forward in support of this view. On the one hand the results following section of the trigeminal have been accounted for in other ways than a direct loss of tone, if I may so call it, in the cornea cells; while the discovery of the vaso-motor nerves has rendered it possible that the phenomena of *herpes zoster* and similar diseases are only indirectly due to the nerves; these latter not governing directly the cell metabolism, but merely, through the blood-vessels, their food supply. On this point Heidenhain's recent work on the salivary glands is of great importance.

As I have already pointed out, a certain amount of nutritive metabolism goes on in every living cell. No matter how specialized its func-

tions in other points, it must ultimately take up from outside and build up for itself new materials to replace those broken down. The Chinese mandarin described by Robinson Crusoe had servants to lift the food to his mouth, but even he had to swallow and digest it for himself; and so for all living tissues.

Apart, however, from this general necessary metabolism of all the tissues, we find in the human body certain sets of cells which are metabolic *par excellence*: whose distinctive characteristic is the working of chemical metamorphoses, just as the physiological character of a muscular fibre is its contractility.

Such cells are found in glands, the products of which are true secretions as distinct from transudata; a transudation being a liquid such as that of the pericardium or beneath the arachnoid, which contains no chemical bodies but such as exist in the blood, while a true secretion contains some *specific element*, some body (as mucin or ptyalin) which does not exist in the blood or lymph, and which must therefore have been made in the gland itself.

If we take a survey of the organic world and study the activity of cells in general, it becomes clear that a secreting cell might produce the specific element of a secretion in either one of two ways. It might as a by-result of its living play of forces produce changes in the surrounding medium, or it might build up certain substances in itself and then set them free as the specific elements. Yeast for example in a saccharine solution causes rearrangement into carbon dioxide, alcohol, glycerine and succinic acid of many atoms of carbon, hydrogen and oxygen which previously existed as sugar and which during the metamorphosis were not passed through the living cell. How the latter acts we do not know with certainty, but most probably by picking certain atoms out of the sugar molecule and leaving the rest to fall down into simpler compounds.

On the other hand we find cells forming and storing up in themselves large quantities of substances which they afterwards liberate—starch for instance being formed and laid by in many fruit cells, and afterwards rendered soluble and passed out to nourish the young plant.

Gland cells might give rise to the specific elements of secretions in either of these two ways, and the first question which calls for decision is, in which manner do they work. Do they simply act as ferments (however that is) upon the surrounding medium, or do they form the special bodies which characterise their secretion, first, within their own substance and then liberate them; either disintegrating, or not, themselves at the same time?

At present there is a large and an increasing body of evidence in favor of the second view. There is no doubt some reason to believe that every living cell can act more or less as a ferment upon certain solutions should they come into contact with it. Not always of course as an alcoholic ferment, though even as regards that one fermentative power it seems very generally possessed by vegetable cells, and there is some evidence that alcohol is normally produced in small amount (and presumably by the fermentation of glucose) under the influence of certain of the living tissues of the human body.

As regards, however, distinctively secretory cells the evidence is all the other way. In many cases we can see the specific element collecting in the gland cells before it is set free in the secretion.

In the mammary gland towards the end of pregnancy fatty degeneration of the cells occurs; and the oil of the milk, consisting mainly of butyrine, a fat which does not exist in the blood, is thus formed. In the colostrum of the first few days after parturition we find many gland cells floating, still tolerably intact, and loaded with oil drops. But later, when lactation is more fully established, the fatty metabolism of the cells is more complete and they break down entirely, so that only the butyrine and casein resulting from their destruction are found in the milk, as a sort of detritus of the secreting cells.

In other cases the liberation of the specific element is not attended with the destruction of the cell. Take for instance the pancreas. As you know, its secretion, besides the power of converting starch into glucose and of breaking up neutral fats, is able to digest albuminous substances in an alkaline medium, turning them into dialysable peptones quite similar to those produced by the gastric juice. This albumen digesting or "proteolytic" ferment is called *trypsin*, and its formation in the gland cells can be followed with the microscope.

The pancreas, like the majority of the glands connected with the alimentary canal, has an intermittent activity determined by the presence or absence of food in various parts of the digestive tract. If the organ be taken from a dog which has fasted four and twenty or thirty hours and put into alcohol, and after hardening, thin sections be prepared, stained with carmine and examined, we get specimens of what we may call the "resting gland," a gland which has not been secreting for some time. In these it will be seen that the cells lining the alveoli present two very distinct zones: an outer, next the lumen, which is granular, and does not combine with carmine; and an inner, which is

non-granular, and picks up the coloring matter. The granules are indications of the presence of a trypsin-yielding substance formed in the cells.

If another dog be kept fasting until he has a good appetite and be then allowed to eat as much meat as he will, he will commonly take so much that his stomach will only be emptied at the end of about twenty hours. Now Bernstein's observations show that this period of twenty hours may, so far as the pancreas is concerned, be divided into two. From the time the food enters the stomach and on for about ten hours the gland secretes abundantly, after that the secretion dwindles, and by the end of the second ten hours has nearly ceased. We have then a time during which the gland is working hard, followed by a period in which its activity is very little, but during which it is abundantly supplied with food materials. The pancreas taken from an animal at the end of the first digestion period and prepared for microscopic examination in the way above described, will be found very different from that taken from a dog killed at the end of the second digestive period, and also from the resting gland.

Towards the end of the period of active work the gland cells are diminished in size, and the proportions of the granular and non-granular zones are quite altered. The latter now occupies most of the cell, while the granular non-staining zone is greatly diminished. During secretion there is a growth of the non-granular and a destruction of the granular zone, and the latter process rather exceeding the former, the whole cell is diminished in size.

During the second digestive period, when secretion is languid, exactly a reverse process takes place. The cells increase in size, so as to become larger than those of the resting gland; and this growth is almost entirely due to the granular zone, which now occupies most of the cell.

These facts suggest that during secretion the granular part of the cells is used up, but that simultaneously the deeper non-granular zone is formed from materials yielded by the blood, and gradually gives rise to the granular. But during active secretion the breaking down of the latter to yield the specific elements occurs faster than its regeneration. In a later period, however, when the secretion is ceasing, the whole cell grows, and at the same time the granular zone is formed faster than it is disintegrated, and hence the great increase of that part of the cell.

If this be so, then we ought to find some relationship between the digestive activity of an infusion or extract of the gland and the size of

the granular zones of the cells, and Heidenhain has shown that such exists; the quantity of trypsin which can be obtained from a pancreas being proportionate to the size of the granular zone of its cells. The trypsin, however, does not exist in these latter ready formed, but only a body which yields it under certain circumstances, and which Heidenhain calls the *zymogen*.

If a perfectly fresh pancreas be divided into halves, and one portion immediately minced and extracted with glycerine, while the other is laid aside for twenty-four hours in a warm place and then similarly treated, it will be found that the first glycerine extract has no proteolytic power whatever, while the second is very active. In other words, the gland does not contain trypsin, but only something which can yield it. The inactive glycerine extract, however, is rich in zymogen, and if a little acetic acid be added to it, this is converted rapidly into trypsin, and the extract becomes powerfully digestive.

We may then sum up the life of pancreas cell in this way: It grows by materials derived from the blood, and first laid down in the non-granular zone. This latter, in the ordinary course of the cell life, gives rise to the granular zone; and in this is a store of zymogen. When the gland secretes the zymogen is converted into trypsin and set free in the secretion; but in the resting cell this transformation does not occur. During secretory activity the chemical processes (the metabolisms of the cell) are different from those at other periods, and we have next to consider how this metabolic or trophic change in the life of the cells is brought about.

When the gland is active we know that it is fuller of blood than when at rest; the arteries are dilated and its capillaries gorged so that it gets a pink color; and this extra blood supply might be the primary cause of the altered metabolism.

On the other hand the activity of the pancreas is under the influence of the nervous system, as evinced not only by the reflex secretion called forth when food enters the stomach, but also by the fact that electrical stimulation of the medulla oblongata will cause the gland to secrete. The nervous system may, however, only act by governing the calibre of the gland arteries, and so but indirectly on the secretory cells; but on the other hand it is possible that nerve fibres act directly upon the gland cells and control their nutritive processes.

To decide the relative importance of these possible agencies we must pass to the consideration of other glands; since the position of the pancreas and the difficulty of getting at its nerves without such severe oper-

ations as upset the physiological condition of the animal, furnish obstacles to its study which have not yet been overcome.

In certain other glands, however, we find conclusive evidence of a direct action of nerve fibres upon secreting elements.

If the sciatic of a cat be stimulated the balls of its feet will sweat. Under ordinary circumstances they become at the same time red and full of blood, but that this congestion is a factor of subsidiary importance as regards secretion is proved by the facts that stimulation of the nerve is still able to cause sweating in a limb which has been amputated ten or fifteen minutes, and in which therefore no circulatory changes can occur; and also by the cold sweats, with a pallid skin, of phthisis and the death agony.

It is however with reference to the sublingual and parotid glands that our information is most precise; thanks mainly to Bernard, Ludwig, and of late years especially to Heidenhain, whose contributions to the physiology of secretion are of the highest value.

When the mouth is empty and the jaws at rest the salivary secretion is little abundant, but a sapid substance placed on the tongue will cause a copious flow. The phenomenon is closely comparable to the production of a reflex movement. A stimulus acting upon an irritable tissue excites through it certain efferent nerve fibres; these excite a nerve centre, which in turn stimulates efferent fibres, going to a muscle in the one case, to a gland in the other. It will be useful to consider for a moment the case of a muscle, taking account only of the efferent fibres and the parts they act upon.

When a muscle in the body is made to contract reflexly or otherwise, through its nerve, two events occur in it. One is the shortening of the muscular fibres; the other is the dilatation of the muscular arteries, so that more blood flows through the organ. Every muscular nerve in fact contains two sets of fibres, one motor and one vaso-dilator, and normally both act together. In this case, however, it is clear that the activities of both, though correlated, are essentially independent. The contraction is not due to the greater blood flow, for not only can an excised muscle, entirely deprived of blood, be made to contract by stimulating its nerve, but in an animal to which a small dose of curari has been given, stimulation of the muscular nerve will cause the vascular dilatation but no contraction; the curari paralyzing the motor fibres, but, unless in large doses, leaving the vaso-dilators intact. The muscular fibres themselves are quite unacted upon by the poison, as evinced by their ready contraction when directly stimulated.

Now let us return to the salivary glands and see how far the facts are comparable. If the *chorda tympani* nerve of a dog be divided and a canula placed in Wharton's duct no saliva will be found to flow. But on stimulating the peripheral end of the nerve an abundant secretion takes place. At the same time, as Bernard showed, there is a great dilatation of the arterioles of the gland, much more blood than previously flowing through it in a given time; the chorda obviously contains vaso-dilator fibres. In this case it might very well be that the process was different from that seen in a muscle. It is conceivable that the secretion might be but a filtration due to the increased pressure in the gland capillaries, consequent on dilatation of the arteries supplying them. If a greater filtration into the lymph spaces of the gland took place this liquid might then merely ooze on through the secreting cells into the commencing ducts, and as it passed through dissolve out and carry on from the cells the specific organic elements of the secretion. Of these, in the submaxillary of the dog at least, mucin is the most important and abundant.

That, however, the process is quite different, and that there are in the gland true secretory fibres, in addition to the vaso-dilator, just as in the muscle there are true motor fibres, has been proved by Ludwig and Heidenhain.

If the flow of liquid from the excited gland were merely the outcome of a filtration dependent on increased blood pressure in it, then it is clear that the pressure of the secretion in the duct could never rise above the pressure in the blood-vessels of the gland. Now experiment shows that the gland can be made to secrete in a recently decapitated animal, in which of course there is no blood pressure; and that when the circulation is going on, the pressure in the duct can rise far beyond that in the gland arteries. Since arterial pressure constantly diminishes from the heart to the capillaries, that in the carotid trunk must be greater than that in the twigs from its facial branch which supply the gland, and Ludwig has shown that if a manometer be connected with the carotid on one side of the neck, and another with Wharton's duct on the other side, then by continued stimulation of the chorda, the pressure of the secretion in the duct can be raised far above that exhibited by the blood in the carotid. Obviously then the secretion is no question of mere filtration, since a liquid cannot filter against a higher pressure.

Finally Heidenhain completed the proof that the vascular dilatation is quite a subsidiary phenomenon. He showed that we could produce all the increased blood flow through the gland without getting any secretion.

That just as in a muscle nerve we can by curari paralyze the motor fibres and leave the vaso-dilators intact, so we can by atropia get similar phenomena in the gland. In an atropised animal stimulation of the chorda will produce vascular dilatation but not a drop of secretion, so that something more than increased blood flow is wanted. Bringing blood to the cells abundantly will not make them drink. We must seek something else in the chorda besides the vaso-dilator fibres, and this something else must be secretory fibres. That the poison acts upon them and not upon the gland cells is shown, as in the muscle, by the fact that the cells still are capable of activity when stimulated otherwise than through the chorda tympani, for example by stimulation of the sympathetic fibres going to the gland.

So far then we seem to have good evidence of a direct action of nerve fibres upon the gland cells. But that is not the whole matter. Heidenhain has recently shown, to my mind conclusively, that there are two sets of secretory fibres in the gland nerves; a set which so acts upon the cells as to make them pass on abundantly the transudation elements of the secretion, the water and mineral salts; and another, quite different, which governs the chemical transformations of the cells, so as to make them produce mucin from matters previously stored in them; in a comparable way to the production of trypsin from zymogen in the active pancreas. These latter fibres he calls "trophic," since they directly control the cell metabolism; while the former he calls "secretory fibres" proper.

Some of the evidence which leads to this conclusion is a little complex. In the first place, about eleven years ago, he showed that on stimulation of the chorda of an unexhausted gland (that is a gland not over-fatigued by previous work) the following points could be noted:—With increasing strength of the stimulus the quantity of the secretion, that is of the water, poured out in a unit of time increases; but at the same time the mineral salts also increase, but more rapidly, so that their percentage in a rapidly formed secretion is greater than in a more slowly formed, up to a certain limit. At the same time the percentage of organic constituents of the secretion also increases up to a limit, but soon ceases to rise, or even falls again, while the water and salts still increase. This of course is readily intelligible; since the water and salts can be derived continually from the blood, while the specific elements, coming from the gland cells, may be soon exhausted. So far then the experiment gives no evidence of the existence of distinct nerve fibres for the salts and water and for the specific elements; both vary together with the strength of the

stimulus applied to the nerve. But under slightly different circumstances their quantities do not run parallel. The proportion of specific elements in the secretion is largely dependent on whether the gland has been previously excited or not. Previous stimulation, not carried on of course to exhaustion, largely increases the percentage of organic matters in the secretion due to a subsequent stimulation, but has no effect whatever on the quantity of water or salts. These are governed entirely by the strength of the second stimulation.

Here then we find that under similar circumstances the transudatory and specific elements of the secretion do not vary together, and are therefore probably dependent upon different causes. And the facts led Heidenhain to conclude that there were in the chorda, besides the vasodilator, two other sets of fibres: one governing the salts and water, and the other the specific elements of secretion.

The evidence was not, however, conclusive, but his more recent experiments upon the parotid gland of the dog have put the matter beyond a doubt.

The submaxillary gland gets not only fibres from the facial nerve through the chorda, but also fibres from the sympathetic. Stimulation of either nerve causes a secretion, that due to the chorda being in the dog abundant, comparatively poor in organic constituents, and accompanied by vascular dilatation; while the "sympathetic saliva," as it is called, is less abundant, very rich in mucin, and accompanied with constriction of the gland arteries. According to Heidenhain's view the chorda contained many secretory and few trophic fibres, and the sympathetic many trophic and few secretory.

It was still, however, possible to object that the greater richness in organic bodies of sympathetic saliva was really due to the small quantity of blood reaching the gland when that nerve was stimulated. This might alter the nutritive phenomena of the cells and cause them to form mucin in unusual abundance, in which case the trophic influence of the nerve would be only indirect.

Experiments on the parotid, however, preclude this explanation. That gland, like the submaxillary, gets nerve fibres from two sources, a cerebral and a sympathetic. The latter enter the gland along its artery, while the former, originating from the glosso-pharyngeal, run in its tympanic branch (the nerve of Jacobson) to the large superficial petrosal, and thence through the otic ganglion and the facial nerve to the gland. Stimulation of the nerve of Jacobson causes an abundant secretion, rich

in water and salt, but with hardly any organic constituents. At the same time it causes dilatation of the gland arteries.

Stimulation of the sympathetic causes contraction of the gland arteries, but no secretion at all. Nevertheless it causes great changes in the gland cells; it contains many trophic fibres, but no secretory. If it be stimulated for a while, and then the nerve of Jacobson, the resulting secretion may be ten times as rich in organic bodies as that obtained without previous stimulation of the sympathetic. And a similar phenomenon is observed if the nerve of Jacobson and the sympathetic be stimulated simultaneously. So that the latter nerve, though unable of itself to cause a secretion, brings about great chemical changes in the gland cells.

This conclusion is confirmed by histology. Sections of the gland after prolonged stimulation of the sympathetic show its cells quite altered in appearance and in their relations to carmine, when compared either with those of the resting gland, or of the gland which has been made to secrete by stimulating the nerve of Jacobson alone.

We have still, however, to meet the objection that the sympathetic fibres may be only indirectly trophic, governing the metabolism of the cells through the blood-vessels. If this be so, then cutting off or diminishing the blood supply of the gland in any way ought to have the same result as stimulation of its sympathetic fibres. Experiment shows that such is not the case and reduces us to a direct trophic influence of the nerve.

Heidenhain ligatured both subclavians in a dog and then exposed the carotids so that they could be clamped or left open at will. When they were closed of course the blood supply to the gland was very nearly (but, in the dog, not quite) cut off. On then stimulating the nerve of Jacobson he found the percentage of organic constituents in the secretion was as low as usual, and was almost exactly the same whether the carotids were open or closed or had been previously open or closed. We must conclude that the peculiar influence of the sympathetic does not depend upon its vaso-constrictor fibres. These observations make it clear that the views until recently commonly held as to the theory of secretion must be considerably modified, at least for the salivary glands, and presumably for others; and they also throw considerable light upon the relationships of the nervous system to cell metabolism. Time forbids me to enter upon a full discussion of the question, and I must confine myself to briefly stating Heidenhain's conclusions.

Let us suppose in the resting gland cells a quantity of material to be formed which has a considerable attraction for water; that this is the product of the nutritive processes of the resting cells. These will, as a result, absorb through the *membrana propria* a quantity of water from the surrounding lymph sinuses; and this will accumulate in each cell until its tension equals the endosmotic force which tends to bring it in. The cell will then be in equilibrium and thus will last as long as the gland is at rest. The water is at a high tension in the cell, but its passage out into the duct and its replacement by more from the lymph is prevented by the limiting layer of the cell protoplasm, the layer bounding it next the lumen of the alveolus. If now a secretory fibre acts upon the cell, the molecular arrangement of this limiting layer is altered, its resistance to filtration or osmosis being diminished. That this is no extravagant supposition is evident from the fact that a nerve fibre can, we know, bring about entirely new molecular arrangements in other tissues, as for instance in a muscular fibre. In consequence of the diminished resistance, some of the water accumulated in the cell will flow into the duct; the cell perhaps actively contracting at the same time and forcing it out, for Kühne has observed active contractions in the cells of the living pancreas of the rabbit. The passage of water from the cells will lower the tension within them, and the cell will again supply itself through its deeper side from the lymph. The lymph in turn will recuperate its losses from the blood; and so long as the gland is secreting, a transference of water from the blood to the gland duct will go on. When the stimulation ceases the molecules of the limiting layer of protoplasm will resume their original arrangement and again oppose a great resistance to filtration. The cell will again fill up with water until equilibrium is attained, and so return to its resting state.

By such means we would obtain a secretion the quantity of which would be quite independent of the percentage of organic matters in it; these, by supposition, existing in such condition within the cells that they remain behind when the water passes out through the limiting layer. In this way also the secretion would be independent of the blood pressure. The pressure which it could attain would depend upon the endosmotic equivalent of the cell substance, the force with which it tended to take up matters from the lymph and then to pass them out by contraction or otherwise into the gland ducts. To explain the increased percentage of salts in the more abundant secretion following a more powerful stimulus, we must suppose also that the molecular rearrangements brought about

are such as to render more easy the passage of saline particles, a supposition which is quite in accord with well known physical facts; the quantity of a salt dialysing through a membrane under given conditions in a certain time being largely dependent upon the molecular structure of the membrane. On this view then the secretory fibres are regarded as simply causing physical molecular rearrangements in the cell, but no important chemical changes.

Turning now to the trophic fibres, we have seen that under their influence soluble organic bodies arise in the gland cells; substances which can be carried out by the water and salines passing through them under the influence of the proper secretory fibres, and which then form the specific elements of the secretion.

The histological and microchemical comparison of the gland which has and that which has not had its trophic fibres stimulated shows that quite different substances accumulate in the cells in the two cases. The resting parotid cells do not form mucin; but when the sympathetic fibres are stimulated, new nutritive processes occur by which mucin is formed abundantly. The action of these fibres is essentially one on the chemical metabolism of the cells—on the very inner processes of cell life. Heidenhain believes that the change effected by the trophic fibres is so profound that on subsequent or simultaneous secretion, the whole cell goes to the ground, being disintegrated as the mammary gland cells are in the formation of milk; while at the same time other more peripheral cells at points in the alveoli multiply rapidly and form new secreting cells. This does not, however, appear to be conclusively established: if it be correct, we would have a state of things answering to that in the beehive where certain individuals doing the work of the community have lost the power of reproduction.

In either case we have evidence of a profound and direct influence exerted by the nervous system upon the nutritive phenomena of cell life; a point which I venture to think has a great pathological importance. If we can directly prove that the chemical phenomena of any one group of cells are controlled by trophic nerve fibres, we establish an *a priori* probability of a similar action in other cases. And the views recently promulgated as to thermal nerves, that is fibres which independently of the blood-vessels can control the oxidation and heat development going on in cells, acquire a considerable collateral support. Should further investigation bring to light more facts similar to those which I have had the honor to lay before you, the whole cellular pathology as at

present understood must, I think, undergo very considerable modification. Fundamentally of course the mode of life of the cell will be determined by what I have called its physiological character; but we shall have also to take largely into account its possible control by an immediate action of the nervous system.

In another way the physiology of secreting cells seems to me to have important pathological significance. It seems to show how absolutely, one might almost say, the activity of a cell is independent of the circulation in its neighborhood. The presence of an abundant blood supply, a congestion of a muscle or a gland, will not throw either organ into activity. One may of course starve a cell by cutting off its blood, or poison it by noxious bodies in that liquid; but apart from such extreme influences, plenty of food will not make a cell work in the absence of some other stimulus to exertion, any more than it will make the whole man.

In its ultimate results I believe there has been no more pernicious error than that made when Davy, experimenting with impure gases, stated that inhalation of pure oxygen, in other words richly supplying the tissues with that element, caused mental exhilaration, febrile phenomena and other signs of increased bodily metabolism. In spite of the most conclusive proof to the contrary, the statement is only just beginning to go out of some of the common text-books of physiology, and it is hard to say when it will cease to be a popular belief.

So long as that belief holds ground, the influence of the circulation upon the life of the tissues must be ever liable to be overrated, and will find its pathological outcome in such beliefs, for instance, as that active cerebral congestion will cause mental excitement. Speaking as a physiologist, and therefore subject to correction from those who have made pathology a special subject of study, I can only say that the belief has no physiological basis whatever, is even directly opposed to all that we know of cell life. There is no evidence that such congestion is the cause of the delirium any more than that of a digesting pancreas or a contracting muscle is the cause of the activity of either; all that we do know as physiologists goes to show that the vascular dilatation is a purely collateral and subsidiary phenomenon in each case. It may have secondary results, and of course pathological congestion often has, and very serious ones; but the primary and immediately acting excitant of the increased tissue activity is in each case to be sought elsewhere.

It is possible, indeed probable, that many of you here present, concerned in the daily observation of disease, are in possession of facts which

are beyond my reach, and will lead you to dissent from the opinions I have just expressed. If however I can lead you to accept, supposing any of you previously doubted it, the belief that physiological experiment affords at least suggestive material for pathological work and thought, I shall have largely gained an end which is naturally very dear to me. The science of physiology is the child of the medical profession; and if in late years it, with its growth and development, tends to assert its claims to existence as an independent science, it is in no spirit of arrogance or self-seeking. Its gains are in the long run your gains, and handed over to you in no grudging spirit. In return you can do much for physiology, not only by close pathological observation, but in other ways, and the debt of honor has hitherto been nobly paid.

A few years ago the medical men of England, by their united action, saved English physiology from extinction. But a combined attack, based in part upon benevolent ignorance, in part upon fanatic misrepresentation (I nearly said lying), and largely upon a passionate hatred of science, especially biological science, which possesses a large section of the English public, led to legislation which must tend to make English speaking physiology find its future home and centre on this side of the Atlantic. Should similar circumstances arise here, it rests with you, exerting that vast influence upon public opinion and enlightenment which the medical man possesses, to secure the freedom and advance of physiology, the triumph of reason over prejudice—of knowledge over ignorance.

XIX.

MODERN PHYSIOLOGICAL LABORATORIES—WHAT THEY ARE AND WHY THEY ARE.

AN ADDRESS DELIVERED ON THE OCCASION OF THE FORMAL OPENING OF
THE NEW BIOLOGICAL LABORATORY OF THE JOHNS HOPKINS
UNIVERSITY, JANUARY 2, 1884.

[Johns Hopkins University Circulars, Vol. III, No. 30, April, 1884.]

A little more than seven years ago I announced from this platform that the old biological laboratory was ready for use,—that set of rooms in the third story of this building, which, inconvenient in many respects as it was, will, I trust, always be remembered by some of us with affection, and mayhap with a little pride.

This night on which we have met to celebrate the completion of the new laboratory is an occasion for looking forward rather than back. But before proceeding to speak in detail of the new building, I feel sure I do what every one of the members of the biological department present would think me remiss to omit, in pausing a moment to express our gratitude to those to whom we owe it,—first to our founder, Johns Hopkins, for his munificence; and next to his trustees. Probably very few present realize how much time and thought the trustees spent on the building before a stone of the foundation was laid, and during its erection. No one but myself knows how often I have been put in good heart by the cheering words, “Well, Dr. Martin, let us get it right when we are about it.” In this connection I cannot refrain from saying, that while we owe all so much, we owe a special debt of gratitude to Mr. J. Hall Pleasants, the chairman of the building committee. Throughout the summer there was hardly a morning on which he did not visit the building; and that not merely for a glance, but far more often to spend an hour or two hours in or about it, and make sure that all was going right.

The material result of this liberality, forethought and supervision is that stately building on the top of the hill. Handsome though not ostentatious, comfortable but not luxurious, pleasant to work in without

unnecessary finery, it stands there, for its purpose unrivalled in the United States, and not surpassed in the world.

Substantial, solid, well thought out, suited to its ends, and with no frippery about it, it is now for the biologists to see that their work agrees in character with the building.

There are many here to-night who, not being biologists, may desire to know what such laboratories are for, and why there is any need of them. I shall perhaps best begin my attempt to answer these questions by stating briefly what our own laboratory is.

It is a building constructed primarily to afford facilities for instruction and research in physiology; and secondarily, similar opportunities in allied sciences, as comparative anatomy and botany, some training in which is essential (and the more the better) to every one who would attain any real knowledge of physiology. As so many distinct branches of biological science are pursued in it, we call it in general the biological laboratory; but it is a biological laboratory deliberately planned that physiology in it shall be queen, and the rest her handmaids. If, therefore, you visit the building prepared to see a great zoological museum or an extensive herbarium, you will be disappointed. I do not underrate, and no one connected with this university can,—having in mind the brilliant anatomical researches of Dr. Brooks and others, made among us,—the claims of morphology; and in time I trust we may see a sister building specially designed for study of the structure, forms and development of plants and animals. But one or the other had to be first chosen unless we were to do two things imperfectly instead of one well, and there were strong reasons for selecting physiology. In the first place, I think even the morphologists will admit that hitherto, and especially in the United States, they have had rather more than their fair share; numerous museums and laboratories have been built for their use; while physiology, if she got anything, has been usually allotted some out-of-the-way room in an entirely unsuitable building, if no one else wanted it; and been very glad to get even that. A second and still stronger reason is, that as medicine is slowly passing out of the regions of empiricism and rule-of-thumb treatment or mal-treatment, it has become evident that sound physiology is its foundation; and this university will at no distant day have a medical school connected with it.

As you walk presently through the rooms of the new building, and see the many instruments of precision for teaching and research—the

batteries, galvanometers, induction-coils and spectroscopes; the balances, reagents and other appliances of a chemical laboratory; the microscope for every student; the library of biological books and journals; the photographic appliances; the workshop for the construction and repair of instruments—when you see these things it may interest you to recall that sixty years ago there was not a single public physiological laboratory in the world; nor was there then, even in any medical school, a special professor of physiology. So late as 1856 Johannes Muller taught in Berlin human anatomy, comparative anatomy, pathological anatomy, physiology, and embryology.

DuBois-Reymond, now himself professor in Berlin, has graphically described the difficulties of the earnest student of physiology, when he attended Muller's lectures in 1840.*

“We were shown a few freshly-prepared microscopic specimens (the art of putting up permanent preparations being still unknown), and the circulation of the blood in the frog's web.” So much for the histological side.

“We were all also shown the experiment of filtering frog's blood to get a colorless clot, an experiment on the roots of the spinal nerves, some reflex movements in a frog, and that opium-poisoning was not conducted along the nerves. There were some better experiments on the physiology of voice,—a subject on which Müller had recently been working; and there was finally a demonstration of the effect upon respiration of dividing the pneumogastric nerves.”

In all, you see six experiments or sets of experiments, in the whole course, in addition to the exhibition of some microscopic slides; and all these mere demonstrations. It was hardly thought of that a student should use a microscope, or make an experiment, himself. If he desired to do so, the difficulties in his way were such as but few overcame.

“He must experiment in his own lodgings, where on account of his frogs he usually got into trouble with the landlady, and where many researches were impossible—there were no trained assistants to guide him—no public physiological library—no collection of apparatus. We had to roll our own coils, solder our own galvanic elements, make even our own rubber tubing, for at that time it was not an article of commerce. We sawed, planed and drilled—we filed, turned and polished. If through the kindness of a teacher a piece of apparatus was lent to us, how we made the most of it—how we studied its idiosyncrasies—above all, how we kept it clean.”

* Emil DuBois-Reymond. *Der physiologische Unterrichte sonst und jetzt*. Berlin, 1878. The quotations from this pamphlet, while giving, I trust, a true idea of the substance of DuBois-Reymond's statements, have been curtailed, and are not to be regarded as literal full translations of the original.—H. N. M.

Of course certain men, the men who were born to become physiologists, and not mere students of physiology, surmounted these difficulties. One has only to recall the names of DuBois-Reymond himself, and of his contemporaries, Brücke, Helmholtz, Ludwig, Vierordt, Donders and Claude Bernard, to realize that fact: and undoubtedly there was a good side to it all. Triflers were eliminated; and the class of individuals was unknown who sometimes turn up at modern laboratories (and judging from a good deal of current physiological literature, sometimes get admitted to them) with a burning desire to undertake forthwith a complicated research, though they hardly know an ordinary physiological instrument when they see it; much less know how to handle it. But they cannot wait; they must begin the next morning, believing, I presume, that laboratories are stocked with automatic apparatus,—some sort of physiological sausage-machines, in which you put an animal at one end, turn the handle, and get out a valuable discovery at the other.

With one exception, Berlin was not in 1840 worse off than other German universities so far as facilities for physiological study were concerned, and certainly better off than any university in England or the United States. The exception was in Breslau, where the celebrated Purkinje, single-handed, had founded a physiological institute. It has usually been supposed that in this he followed the example of Liebig, who founded at Giessen the first public chemical laboratory; but this, *pace* the chemists, can hardly have been the case. It is to Purkinje that the honor belongs of founding the first public laboratory. Liebig undoubtedly conceived the plan when working in Paris in Gay Lussac's private laboratory, but it was not until 1826 that he began to put it into execution; and at that date Purkinje had already, largely at his own cost, started a physiological laboratory at Breslau, open to students—on a small scale, it is true, but still the germ of all those great laboratories of physics, chemistry and biology, which are now found in every civilized country, and to which more than to anything else, modern science owes its rapid progress. Of these there must be at least forty now organized for physiological work; and almost every year sees an increase in their number. How has this come about in the fifty-odd years which have passed since the opening of Purkinje's poorly-equipped and little known work-rooms?

First, because of the improvement in philosophy which took place when men began to break loose from the trammels of mediaeval metaphysics, and to realize that a process is not explained by the arbitrary assumption of some hypothetical cause invented to account for it. So long

as the phenomena exhibited by living things were regarded, not as manifestations of the properties of the kind of matter of which they were composed, but as exhibitions of the activity of an extrinsic independent entity—a *pneuma*, *anima*, *vital spirit*, or *vital principle* which had temporarily taken up its residence in the body of an animal, but had no more essential connection with that body than a tenant with the house in which he lives,—there was no need for physiological laboratories. Dissection of the dead body might, indeed, be interesting as making known the sort of machine through which the vital force worked,—just as some people find it amusing to visit the former abode of a great author, and see his library and writing-table and inkstand; and there might be discussions as to the locality of the body in which this vital force resided; to carry out our simile, as to what was its favorite armchair. Various guessers placed it in the heart, the lungs, the blood, the brain, and so forth. Paracelsus, with more show of reason, located it in close connection with the stomach, on the top of which he supposed there was seated a chief vital spirit, *Archaeus*, who superintended digestion. It is mainly to Descartes,* who lived in the earlier half of the seventeenth century, that physiology owes the impulse which set it free from such will-o'-the-wisps. Putting aside all consciousness as the function of the soul, he maintained that all other vital phenomena were due to properties of the material of which the body is composed; and that death was not due to any defect of the soul, but to some alteration or degeneration in some part or parts of the body.

The influence of Descartes, and, in the same half-century, the demonstration of the circulation of the blood by Harvey, gave a great impulse to experimental physiology. Both Harvey and Descartes, however, still believed in a special locally placed vital spirit or *force* which animated the whole bodily frame; as the engine in a great factory moves all the machinery in it. What a muscle did, or a gland did, depended on the structure and properties of the muscle or gland; but the work-power was derived from a force outside those organs,—on vital spirits supplied from the brain along the nerves, or carried to every part in the blood. As the pattern of a carpet depends on the structure and arrangement of the loom,—which loom, however, is worked by a distant steam-engine,—so the results of muscular or glandular activity were believed to be deter-

* See Huxley: *The connection of the biological sciences with medicine* (*The Lancet*, August 13, 1881.)

mined by the structure of muscle and gland; but the moving-force to come from some other part of the body.

The next important advance was made by Haller, about the middle of the eighteenth century. He demonstrated that the contracting power of a muscle did not depend on vital spirits carried to it by nerve or blood, but on properties of the muscle itself. Others had guessed, Haller proved, that the body of one of the higher animals is not a collection of machines worked by a central motor, but a collection of machines each of which is in itself both steam-engine and loom; leaving aside, of course, certain of the purely mechanical supporting and protecting apparatuses of the skeleton. This was the death-blow of the 'vital force' doctrine. Extensions of Haller's method showed that it was possible to destroy the brain and spinal cord of an animal, and separate its muscles, its heart, its nerves, its glands, and yet keep all these isolated organs working as in normal life for many hours. Henceforth the *life* of an animal could not be regarded as an entity residing in one region of the body, from which it animated the rest; the word gradually became a mere convenient phrase for expressing the totality or *resultant* of the actions of the individual organs. Physiologists began to see that they had nothing to do with hunting out a vital force, or with essences or absolutes; that their business was to study the phenomena exhibited by living things, and leave the noumena, if there were such, to amuse metaphysicians. Physiology became more and more a study of the mechanics, physics and chemistry of living organisms and parts of organisms.

Progress at first was necessarily very slow; physics and chemistry, as we now know them, did not exist. Galvanism was not discovered, osmosis was unknown, the conservation of energy was undreamed of; modern chemistry did not take its rise until the discovery of oxygen by Priestley, and the extension and application of that discovery by Lavoisier towards the close of the last century. Physiology had to wait then, as now, for its advance upon the development of the sciences dealing with simpler forms of matter than those found in living things. But little by little, step after step, so many once mysterious vital processes have been explained as but special illustrations of general physical and chemical laws, that now the physiologist scans each advance in chemistry or physics in full confidence that it will enable him to add others to the phenomena of living bodies, which are in ultimate analysis not peculiar or 'vital,' but simply physico-chemical. Apart from the phenomena of mind whose mysterious connection with forms of matter he can never

hope to explain, if a physiologist were to-day asked what is the object of his science, he would answer, "not the discovery or the localization of a vital force, but the study of the quantity of oxidizable food taken into the stomach, and the quantity of oxygen absorbed in the lungs; the calculation of the energy or force liberated by the combination of the food and oxygen; observation of the way in which that force has been expended, the means by which its distribution has been influenced, and the form in which the unused matter, if any, has been stored."

Once it was recognized that the majority of physiological problems were problems admitting of experimental investigation, the necessity for special collections of apparatus suitable for experiment on living plants and animals, and for affording students an opportunity to study the play of forces in living organisms, had not long to wait for recognition. Physiological laboratories were organized: at first in such rooms as could be spared in buildings constructed for other purposes; later, in structures built for this special end. The first laboratory specially erected for physiological work was built for Vierordt, in Tübingen, less than twenty years ago. So far as I know, our own is the first such building in the United States.

There is still another reason which has combined with the recognition of the independence of physiology as a science to make the modern laboratory, open to all properly prepared students, a possibility; and physiology owes it to this country. I do not forget how Brown-Sequard in Philadelphia clinched and completed Bernard's great discovery of the vaso-motor nerves; nor the researches of Weir Mitchell on the functions of nerve-centres, and the action of snake-poisons; nor, in later years, the researches of Wood on the physiology of fever; and, on various subjects, of Bowditch, Arnold, Flint, Minot, Sewall, Ott, Chittenden, Prudden, Keyt, Sedgwick, and others. But speaking with all the diffidence which one, who, at least by birth, is a foreigner, must feel in expressing such an opinion, I say, that considering the accumulated wealth of this country, the energy which throbs throughout it, and the number of its medical schools, it has not done its fair share in advancing physiological knowledge; but for one thing, which makes the world its debtor. I mean the discovery of anaesthetics. When Morton, in 1846, demonstrated in the Massachusetts General Hospital that the inhalation of ether could produce complete insensibility to pain, he laid the foundation-stone of our laboratory, and of many others. No doubt the men whose instincts led them to physiological research, and who realized that by the infliction of

temporary pain on a few of the lower animals they were discovering truths which would lead to alleviation of suffering and prolongation of life, not only in countless generations of such animals themselves, but in men and women to the end of time, would have tried to do their work in any case. But those who can steel their hearts to inflict present pain for future gain are few in number. The discovery of anaesthetics has not only led to ten physiological experimenters for each one who would have worked without them, but by making it possible to introduce into the regular course of physiological teaching demonstrations and experiments on living animals, without shocking the moral sense of students or of the community at large, has contributed incalculably to the progress of physiology.

On the occasion of the opening of the old laboratory I used these words :*

“Physiology is concerned with the phenomena going on in living things, and vital phenomena cannot be observed in dead bodies ; and from what I have said you will have gathered that I intend to employ vivisections in teaching. I want, however, to say, once for all, that here, for teaching purposes, no painful experiment will be performed. Fortunately the vast majority of physiological experiments can now-a-days be performed without the infliction of pain ; either by the administration of some of the many anaesthetics known, or by previous removal of parts of the central nervous system ; and such experiments only will be used here for teaching. With regard to physiological research, the case is different. Happily here, too, the number of necessarily painful experiments is very small indeed ; but in any case where the furtherance of physiological knowledge is at stake—where the progress of that science is concerned, on which all medicine is based, so far as it is not a mere empiricism—I cannot doubt that we have a right to inflict suffering upon the lower animals, always provided that it be reduced to the minimum possible, and that none but competent persons be allowed to undertake such experiments.”

Those words were a declaration of principle, and a pledge given to this community, in which I was about to commence my work. That the work has been carried on for seven years among you, without a murmur of objection reaching my ears, is sufficient proof that Baltimore assents to the principle ; and, gratifying as the building of our new laboratory is to me from many points of view, there is none so grateful as its witness, that, in the opinion of our trustees and of my fellow-citizens, I have carried out my pledge. There has been no hole-and-corner secrecy about the matter ; the students in the laboratory have been no clique

* Popular Science Monthly, December, 1876.

living isolated in a college building; but either your own sons, or boarders scattered among dozens of families in this city; and no room in the laboratory has ever been closed to any student; what we have done has been open to all who cared to know. On this occasion, when we make a fresh start, I desire to re-assert the principle, and repeat the pledge.

We have seen that Haller laid the foundation of our knowledge that the body of one of the higher animals is essentially an aggregation of many organs, each having a sort of life of its own, and in health co-operating harmoniously with others for the common good. In the early part of this century, before scientific thought had freed itself from mediaeval guidance, this doctrine sometimes took fantastic forms. For example, a school arose which taught that each organ represented some one of the lower animals. DuBois-Reymond relates that in 1838 he took down these notes at the lectures of the professor of anthropology :

“ Each organ of the human body answers to a definite animal, is an animal. For example, the freely movable, moist and slippery tongue is a cuttlefish. The bone of the tongue is attached to no other bone in the skeleton; the cuttlefish has only one bone, and consequently this bone is attached to no other. It follows that the tongue is a cuttlefish.”

However, while Professor Steffens and his fellow transcendentalists were theorizing about organs, others were at work studying their structure; and a great step forward was made in the first year of our century by the publication of Bichât's ‘Anatomie générale.’ Bichât showed that the organs of the body were not the ultimate living units, but were made up of a number of different interwoven textures, or *tissues*, each having vital properties of its own. This discovery paved the way for Schwann and Schleiden, who laid the foundation of the cell-theory; and showed, that, in fundamental structure, animals and plants are alike, the tissues of each being essentially made up of aggregates of more or less modified microscopic living units called *cells*. Our own generation has seen this doctrine completed by the demonstration that the essential constituent of the cell is a peculiar form of matter named protoplasm, and that all the essential phenomena of life can be manifested by microscopic bits of this material; that they can move, feed, assimilate, grow, and multiply; and still further, that, wherever we find any characteristic vital activity, we find some variety of protoplasm. Physiology thus has become reduced in general terms to a study of the faculties of protoplasm; and

morphology to a study of the forms which units or aggregates of units of protoplasm, or their products, may assume. The isolation of botany, zoölogy, and physiology, which was threatened through increased division of labor, due to increase of knowledge necessitating a limitation of special study to some one field of biology, was averted; and the reason was given for that principle which we have always insisted upon here—that beginners shall be taught the broad general laws of living matter before they are permitted to engage in the special study of one department of biology.

If I be asked, what have biological science in general and physiology in particular done for mankind to justify the time and money spent on them during the past fifty years, I admit it to be a perfectly fair question; fortunately it is one very easy to answer. Leaving aside the fruitful practical applications of biological knowledge to agriculture and sanitation, I will confine myself to immediate applications of the biological sciences to the advance of the theory, and, as a consequence, of the art of medicine.

So long as the life of a man was believed to be an external something distinct from his body, but residing in it for a while, diseases were naturally regarded as similar extrinsic essences or entities, which invaded the body from without, and fought the 'vital force.' The business of the physician was to drive out the invader without expelling the vital spirits along with it—an unfortunate result, which only too often happened. To the physicians of the sixteenth century a fever was some mysterious extraneous thing, to be bled, or sweated, or starved out of the body, much as the medicine-men of savages try to scare it off by beating tomtoms around the patient. Once life was recognized as the sum-total of the properties of the organs composing the body, such a theory of disease became untenable, and the basis of modern pathology was laid. Disease was no longer a spiritual indivisible essence, but the result of change in the structure of some one or more of the material constituents of the body, leading to abnormal action. The object of the physician became, not to expel an imaginary immaterial enemy, but to restore the altered constituent to its normal condition.

The next great debt which medicine owes to biology is the establishment of the cell-doctrine—of the fact that the body of each one of us is made up of millions of little living units, each with its own properties, and each in health doing its own business in a certain way under certain conditions; and no one cell being more the seat of life than any other.

The activity of certain cells may, indeed, be more fundamentally important to the maintenance of the general life of the aggregate than that of others; but the cells, which, by position or function, are more essential than the rest, are, in final analysis, no more alive than they. Before the acceptance of the cell-doctrine pathologists were practically divided into two camps—those who believed that all disease was primarily due to changes in the nervous system, and those who ascribed it to alteration of the blood. With the publication of Virchow's 'Cellular pathology' all this was changed. Physicians recognized that the blood and nerves might at the outset be all right, and yet disease originate from abnormal growth or action of the cells of various organs. This new pathology, like the older, was for a time carried to excess. We now know that there may be general diseases primarily due to changes in the nervous system, which binds into a solidarity the organs of the body; or of the blood, which nourishes all; but we have also gained the knowledge that very many, if not the majority, of diseases have a local origin, due to local causes, which must be discovered if the disease is to be successfully combated. An engineer, if he find his machinery running imperfectly, may endeavor to overcome this by building a bigger fire in his furnace, and loading the safety-valve. In other words, he may attribute the defect to general causes; and in so far he would resemble the old pathologists. But the skilled engineer would do something different. If he found his machinery going badly, he would not jump forthwith to the conclusion that it was the fault of the furnace, but would examine every bearing and pivot in his machinery, and, only when he found these all in good working order, begin to think the defect lay in the furnace or boiler; and in that he would resemble the modern physician instructed in the cell-doctrine.

A third contribution of biology to medical science is the germ-theory as to the causation of an important group of diseases. To it we owe already antiseptic surgery; and we are all now holding our breath in the fervent expectation that in the near future, by its light, we may be able to fight scarlet-fever, diphtheria, and phthisis, not in the bodies of those we love, but in the breeding-places, in dirt and darkness, of certain microscopic plants.

From one point of view the germ-theory may seem a return to the idea that diseases are external entities which attack the body; but note the difference between this form of the doctrine and the ancient. We are no longer dealing with immaterial, intangible, hypothetical *somethings*; the

modern practitioner says, "Well, show me the bacteria, and then prove that they cause the disease: until you can do that, do not bother me about them."

It is worth while, in passing, to note that these three great advances in medical thought were brought about by researches made without any reference to medicine. Haller's purely physiological research into the properties of muscles laid the foundation of a rational conception of disease. The researches of Schwann on the microscopic structure of plants, and since then researches of others on the structure of the lowest animals, led to the cellular pathology. Antiseptic surgery is based on experiments carried out for the sole purpose of investigating the question as to spontaneous generation. My friend Dr. Billings has described "the languid scientific swell, who thinks it bad style to be practical, and who makes it a point to refrain from any investigations which lead to useful results, lest he might be confounded with mere practical men." Well, I am sorry for the swell! because, for the life of me, I cannot see how he can make any investigations at all. The members of his class must be so few in number that we need not waste much grief on them. I never have met with an investigator who would not be rejoiced to find any truth discovered by him put to practical use; and I feel sure that in this day and generation the chief danger is that disproportionate attention will be devoted to practical applications of discoveries already made, to the exclusion of the search for new truth. So far as physiology is concerned, it has done far more for practical medicine since it began its own independent career, than when it was a mere branch of the medical curriculum. All the history of the physical sciences shows that each of them has contributed to the happiness and welfare of mankind in proportion as it has been pursued by its own methods, for its own ends, by its own disciples. As regards physiology, this is strikingly illustrated by a comparison of the value to medicine of the graduation theses of Parisian and German medical students. A candidate for the doctorate of medicine in France or Germany, as in many schools here, must present a graduation thesis on some subject connected with his studies. Every year a certain number select a physiological topic. The French student usually picks out some problem which appears to have a direct bearing on the diagnosis or treatment of disease, while the German very often takes up some physiological matter which on the surface has nothing to do with medicine. Now, any one who will carefully compare for a series of years the graduation theses in physiology of German and French can-

didates, will discover that even the special practical art of medicine itself is to-day far more indebted to the purely scientific researches of the German students than to those of the French, undertaken with a specific practical end in view. Situated as we shall be here, in close relation to a medical school, and yet not a part of it, I believe we shall be under the best possible conditions for work. Not under too direct pressure from the professional staff and students on the one hand, on the other we shall be kept informed and on the alert as to problems in medicine capable of solution by physiological methods.

I must find time to say a few words as to the connection of physiology with pathology and therapeutics. The business of the physiologist being to gain a thorough knowledge of the properties and functions of every tissue and organ of the body, he has always had for his own purposes to place these tissues under abnormal conditions. To know what a muscle or a gland is, he has to study it not merely in its normal condition, but when heated or cooled, supplied with oxygen or deprived of it, inflamed, or starved; and see how it behaves under the influence of curari, atropine, and other drugs. From the very start of physiological laboratories a good deal of work done in them has necessarily been experimental pathology and experimental therapeutics. I suppose to-day that at least half of the work published from physiological laboratories might be classed under one or other of these heads. And what has been the fruit? I can here refer only to one or two examples. It is not too much to say, that, though inflammation is the commonest and one of the longest studied pathological states, we really knew nothing about it before the experimental researches of Lister, Virchow, and Cohnheim; and that all we really know as to the nature of fever is built on the similar researches of Bernard, Heidenhain, Wood, and others. As to therapeutics, so far as giving doses of medicine is concerned, it, still in its very infancy, had its birth as an exact science in physiological laboratories. Every modern text-book on the subject gives an account of the physiological action of each drug. What the future may have in store for us by pursuit of such inquiries it is hard to limit. The work of Bernard—showing that in curari we had a drug that would pick out of the whole body, and act upon, one special set of tissues, the endings of the nerve-fibres in muscle—and the results of subsequent exact experiments as to the precise action of many drugs upon individual organs or tissues, hold out before us a hope that, perhaps at no very distant day, the physician will know exactly, and in detail, what every drug he puts into his patient is going to do within him.

Pathology and therapeutics, while almost essential branches of physiological inquiry, have nevertheless their own special aims; and, now that the physiologists have proved that it is possible to study these subjects experimentally, special laboratories for their pursuit are being erected in Germany, France, and England. These laboratories are stocked with physiological instruments, and carry on their work by physiological methods. Those who guide them, and those who work in them, must be trained physiologists: if not, the whole business often degenerates into a mere slicing of tumors and putting up of pickled deformities: pathological anatomy is a very good and very important thing in itself, but it is not *pathology*. Looking at the vast field of pathological and therapeutic research open to us, and bearing in mind the certainty of the rich harvest for mankind which will reward those who work on it, I believe it one of my chief duties to prepare in sound physiological doctrine and a knowledge of the methods of experiment, students who will afterwards enter laboratories of experimental pathology and pharmacology immediately connected with a medical school.

If the relations of the biological sciences to medicine be such as I have endeavored to point out, what place should they occupy in the medical curriculum? That men fitted for research, and with opportunity to pursue it, should be trained to that end, is all well and good; but how about the ninety per cent. who want simply to become good practitioners of medicine? What relation is this laboratory to hold to such men, who may come to it, intending afterwards to enter a medical school? As a part of their general college-training, affording that education of a gentleman which every physician should possess, it should give a sound knowledge of the general laws which govern living matter, without troubling students with the minutiae of systematic zoölogy or botany; it should enable them to learn how to dissect, and make them well acquainted with the anatomy of one of the higher animals; it should teach them how to use a microscope; and the technique of histology; and finally, by lectures, demonstrations and experiment, make known to them the broad facts of physiology, the means by which those facts have been ascertained, and the basis on which they rest. The student so trained, while obtaining the mental culture which he would gain from the study of any other science, is especially equipped for the study of medicine. Taught in other parts of his general collegiate course to speak and write his own language correctly, having acquired a fair knowledge of mathematics and Latin, able to read at least French and German,

having learned the elements of physics and chemistry, and in addition, having studied the structure and properties of the healthy body, he can, on entering the technical school, from the very first turn his attention to professional details. Knowing already the anatomy of a cat or a dog, he knows a great part of human anatomy, and need do little but acquaint himself with the surgical and medical anatomy of certain regions. Knowing normal histology, he can at once turn his attention to the microscopy of diseased tissues. Well instructed in physiology, he can devote himself to its practical applications in the diagnosis and treatment of disease. The demand for an improvement in medical education, which has been so loudly heard in England and this country for some years, is (the more I think of it, the more I feel assured) to be met, not, as has been the case in England, by putting more general science into the medical curriculum, but by confining that curriculum to purely professional training, and providing, as we have attempted to do here, non-technical courses for undergraduates, which, while forming part of a liberal education, also have a distinct relation to their future work. I regard it as the most important of my duties, to prepare students to enter medical schools in this city or elsewhere.

To advance our knowledge of the laws of life and health; to inquire into the phenomena and causes of disease; to train investigators in pathology, therapeutics, and sanitary science; to fit men to undertake the study of the art of medicine—these are the main objects of our laboratory. I do not know that they can be better summed up than in the words of Descartes, which I would like to see engraved over its portal: "If there is any means of getting a medical theory based on infallible demonstrations, that is what I am now inquiring." (*Reprinted from Science, January 18, 25, 1884.*)

XX.

THE STUDY OF THE PHYSIOLOGICAL ACTION OF DRUGS.

ANNUAL ADDRESS DELIVERED AT THE EIGHTY-SEVENTH ANNUAL
CONVENTION OF THE MEDICAL AND CHIRURGICAL FACULTY
OF MARYLAND.

[*Transactions of the Medical and Chirurgical Faculty of Maryland, 1885.*]

Some years ago I was present when some young officers were being instructed and examined by the adjutant of their regiment. He finally asked "What, in few words, is the object of the education given a soldier?" The answers were varied:—To increase his intelligence, to make him hardy, to render him fearless, to train him in the art of war. But the adjutant still shook his head. At last some one suggested, "To enable him to destroy his enemy." "That is correct," replied the instructor. "The aim of the soldier's training, from the goose-step taught the recruit, to the instruction in the higher mathematics given an artillery officer, is—to enable him to destroy his enemy."

Suppose the question put to a number of medical students about to graduate—what is the object of medical education? How should it be answered? Some might reply, "To enable the doctor to earn a living"; some, "To give him a knowledge of life and living things"; some, "To fit him to increase scientific knowledge of disease"; but overwhelming and drowning all such answers would surely come the chorus "To fit him to practice"; "To enable him to destroy his enemy—*disease*." The practice of medicine, the prevention and cure of disease, is the aim of medical education, from learning the bones to the study of the science of disease, as expounded by a Virchow, a Pasteur, a Cohnheim or a Koch.

When we consider the simple training of the soldier of olden times, and contrast it with the education which enabled a young officer, by observing the stars, to guide Wolseley's army on a moonless night for seven miles, through the winding depressions of a pathless desert, and bring them, before dawn, straight to the enemy's entrenchments at Tel el Kebir, we realize how complex the art of war has become and how dependent on many sciences.

As modern warfare differs from ancient, so does modern medicine from that of the Egyptians or Greeks. The fundamental qualities necessary to success in overcoming the enemy—energy, courage, quickness of perception, fertility of resource—remain the same as ever, but the amount of scientific knowledge (and consequently the fighting power) at the disposal of those who contend, either in our ranks or those of a great military organization, is far greater.

As professors of physics and chemistry, and great laboratories for the scientific study of explosive compounds, are maintained by the military nations of Europe in order that the soldier who goes to the front, rifle in hand, shall be better equipped for the conflict—so dissecting rooms and laboratories of physiology, of pathology, of therapeutics exist that the physician may be aided in his daily struggle against disease.

The main ends sought by those who devote their lives to medical work I have already described as the *prevention* and the *cure* of disease. If I have chosen for this occasion a topic rather connected with cure than prevention, it is not that I think the latter less important; it is surely the goal which our profession must strive to reach—and it is one concerning which the general public is strangely apathetic, unless during periods of panic when an epidemic threatens. Our profession has done its duty in this matter; it remains for the public to perform its share.

When I consider the vast amount of unselfish effort made by physicians to prevent disease—that the medical men in every community are the leaders in sanitary work—that nevertheless such charges are brought against them by the ignorant as that they advocate vaccination because they are paid for performing it and think it will increase disease—when I read of the physicians of Marseilles and Naples assaulted by the mob because they were believed to have introduced cholera—yet going steadfastly on their way to help the sufferers, and risking their lives in experiments to discover the cause as well as the means of preventing this plague—then indeed I feel (and who amongst you does not?) proud of my profession.

You have asked me to address you as one concerned rather with the theory than the practice of the medical arts—as one whose relations to our holy warfare is rather that of him who makes cartridges in the arsenal than of the soldier who handles the gun at the outposts. A chief object of such annual gatherings as this of the Medical and Chirurgical Faculty is to consider in what directions the sciences and the arts of medicine and surgery have advanced; what the practical value of such

advance may be at present—with what hope it cheers us for the future—what department, if any, is lagging behind and should be fostered.

I have selected as my topic *Pharmacology*—that branch of science which is concerned with the investigation of the action of drugs on the healthy body—because I believe that it is destined in the near future to acquire an importance in regard to therapeutics which is not yet properly appreciated.

Pharmacology can hardly be said to have existed in ancient medicine, nor indeed until the present century. The first persons to study experimentally the action of drugs appear to have been those who desired to discover a sure poison for their enemies or a certain antidote for themselves.

The etymology of the word shows that, among the Greeks, medicines were regarded as mysterious things, as substances possessing some magical power, either inherent or imparted by sorcery. *φαρμακος* meant to the Greek the use of drugs, potions or spells. The word *φαρμακεια* indicated alike a physician, a sorcerer, or a poisoner. To-day we find, even in civilized nations, something of this old notion remaining. Medicine is, to a large extent, still regarded by the laity as a mystic art. Seventh sons of seventh sons advertise in the newspapers (no doubt with profit to themselves) that they are prepared, in return for a few dollars, to exercise their magical power for the cure of disease; and many otherwise intelligent persons are gulled by the jargon of those who describe the supernatural virtues of an infinitesimal dose of some drug raised to almost omnipotent power by a seventeenth or a seventieth trituration.

The discovery of useful remedies was, in former times, a matter of accident. There was no organized search for them, nor any rational attempt to reach some hypothesis as to the mode of action of drugs which might give a clue to their usefulness in various pathological conditions.

By multiplied experience the list of medicines was slowly increased. According to Strabo, the Egyptians exposed in the streets persons who were dangerously ill, that passers-by, who had seen some similar case recover, might advise treatment. When we consider how, nowadays, every one has a sure cure for dyspepsia, which he or she recommends as infallible to each sufferer from that multiform disease, we can picture to ourselves the unhappy condition of those Egyptian patients, that is, if they tried to act in accordance with all the advice given them.

However, after repeated trial, some remedies, no doubt, proved useful in certain diseases, and handed down by tradition or recorded by priests, made the beginning of a *materia medica*. Somewhat later in the world's story, in Greece and Rome, the votive tablets describing their disease and its treatment, placed by grateful patients in certain temples, added to the list of medicines which had been tested and found valuable.

In the centuries of mediæval darkness the Arabs did something to advance pharmacology; the Europeans almost nothing. The Egyptians, the Greeks and the Romans had been sound in their method, so far as it went. It was empirical. What they had found to do good before they gave again in a similar disease, as we to-day order quinine in intermittent fever, not because of any knowledge or theory as to its mode of action, but because we have found it more often useful than any other medicine in the treatment of this disease.

In the middle ages, this sound, if narrow Hippocratic method was replaced by pseudo-sciences of the most absurd kind. All sorts of fanciful doctrines as to drugs were allowed to determine their administration, quite regardless of observation or experiment as to their effect. Of such doctrine, that of "signatures" may serve as an example. It originated with Paracelsus in the sixteenth century and had great vogue. According to it, natural objects, especially plants, were given medicinal virtues by the stars, and each bore some mark or signature from which its proper use might be learned. The duty of the physician was to decipher these signatures. Thus the houseleek resembles the gums in the texture of its leaves, hence is a valuable remedy for scurvy; the root of the hedgeturnip is like a swollen foot—a sure sign that it is a cure for dropsy; the eyes on a peacock's tail, resembling the nipple of the female surrounded by its areola, are clearly indicated for diseases of the breast. How widespread this doctrine was is indicated by the many European plants which owe to it their names, both common and scientific. The lungwort, still known to botanists as *Pulmonaria*, owes its name to the belief that the grayish mottled appearance of its petals (somewhat resembling a tuberculous lung) indicated it as a specific for phthisis; the liverworts or *Hepaticæ* have a peculiarly marked epidermis, which suggests the outlines of the liver lobules, hence were used in liver disease. A species of *Aristolochia* is still known in England as "birthwort." It has a corolla whose opening suggests the form of the female pudendum when dilated. Infusions or decoctions of it were given with great faith in their efficacy in all cases of labor. To those who objected that experience had proven these plants

and animals not to have the virtues attributed them, the advocates of the doctrine of signatures replied that to deny it was to call God a liar—a mode of argument not yet entirely given up by those who would have us read the book of Nature through the spectacles of some preconception, rather than by patient, unbiased and reverential observation and experiment.

Even at the end of the seventeenth century we find in the London Pharmacopœia, issued by the Royal College of Physicians, such drugs as crab's eyes, pearls, oyster-shell and coral. All of these are of course nothing but somewhat impure calcium carbonate, such action on the body as they may exert being the same as that of chalk. But each one, on account of fantastic notions concerning the animal it was derived from, and the nature of disease, was imagined to have very different therapeutic properties. The doctor who should prescribe crab's eyes when tradition ordered oyster-shell would surely have been held guilty of malpraxis.

Other drugs found in this pharmacopœia are the excrement of mice, of the dog and of the goose; calculi; moss which had grown on the human skull—clearly a most precious remedy, for even in the edition of 1721, edited by Sir Hans Sloane, and a great improvement on its predecessors, this moss is retained, as also dog's excrement and earthworms.

While physicians believed on mere *a priori* grounds, apart from all serious study of facts or any attempts at experimental investigation, that such drugs had a special and mysterious efficacy in certain diseases; while the therapeutical value of a vegetable preparation was believed to depend largely on whether the leaves had been gathered during the conjunction of Venus and Jupiter; while tradition, not observation, was the basis of medical practice, pharmacology could not be born. Even after Sydenham, the father of modern English and American medicine, had led the way back to Hippocratic methods, pharmacology had still to wait—to wait until chemistry could supply pure drugs, and experimental physiology had taught us how to set about examining their action on various organs and tissues.

Bichât, when he pointed out, early in the present century, that all organs were composed of several tissues, and that some of these might be diseased and others healthy, seems to have also noted that the action of drugs on different tissues and organs needed study. His early death prevented him from undertaking such investigations. The first real pharmacological research was made by his great pupil, Magendie. Its

subject was strychnia, and since his work is an excellent example of the investigation of the physiological action of a drug, and as our reasons for prescribing this remedy in certain diseased states and avoiding it in others are based on Magendie's work, I shall give an account of his investigation in some detail. What Magendie actually used was upas, a poison known to cause convulsions and death, and suspected to act on the spinal cord. It was shortly afterwards proved that the active principle of upas was strychnia. To avoid confusion I shall speak as if Magendie had worked with that alkaloid. Magendie's research was undertaken to discover whether this substance could be proved experimentally to have a special affinity for and a specific action on some one organ.

It is almost incredible to us now that but sixty years ago this had not been proved for a single medicine. That Epsom salts purged and squills caused diuresis was well known, but there had been made no attempt to ascertain the method of action of either. The knowledge now at the physician's disposal, which enables him to select a purgative or a diuretic according to the pathological state of his patient, was entirely wanting. The reasons which to-day guide us to choose digitalis as a diuretic in some cases of dropsy, and squills or nitrous ether in others, did not exist.

Magendie's plan* was very simple. It was not exactly the method which we would now employ as regards details, but it was the same in principle. The symptoms of upas poisoning indicated that the drug acted primarily on the spinal cord. This he tested by administering it under conditions which allowed it to reach quickly all organs of the body except the spinal cord. The result was that convulsions did not occur until sufficient time had elapsed for the poison to be carried by the blood to the cord, but then they appeared. Next he applied the poison to the spinal cord alone; this caused convulsions almost at once, but first of all in the regions of the body supplied by nerves arising from the segment of the spinal cord on which the upas was placed. Next he gave the poison after destroying the spinal cord and found that no convulsions resulted. Finally, he administered it and, after convulsions had commenced, gradually destroyed the spinal marrow from above down. As this was done the tetanus disappeared, first in the fore limbs and anterior regions of the trunk, then in the belly muscles, finally in those of the hind legs and tail. When the whole cord was destroyed all the convul-

* Lauder Brunton, *Pharmacology and Therapeutics*, page 74.

sions ceased. Magendie concluded that upas was a spinal excitant, a conclusion which subsequent investigation has abundantly confirmed.

His next idea was that practical medicine might be aided by a drug which was a specific stimulant of the spinal cord, for, as he points out, many serious diseases are due to defective activity of that organ. But unfortunately upas was not an article of commerce, and should it be found a valuable therapeutic agent there still remained the problem, How to get it?

This problem Magendie tried to answer by investigating the physiological action of extract of *nux vomica*, a plant belonging to the same natural order as the upas tree, and readily purchasable.

He found this extract to act exactly like the upas, and it consequently came to be used in certain cases of paralysis, especially in cases of what we would now name defective reflex excitability.

Fonguier, incited by Magendie's discovery, appears to have been the first to use the new medicine in such diseases. Magendie afterwards prescribed it with benefit to his own patients, and it is now recognized as one of our most valuable therapeutic agents.

To-day we order strychnia, the active principle, rather than the crude drug, but our knowledge of its activity and our ability to select the cases in which its administration is advisable are due to Magendie's research.

From strychnia, the most potent exaltant of reflex excitability, let us pass on to consider briefly *chloral*, a powerful depressant.

In this valuable, though in the hands of the laity often abused, medicine we have a remedy which we owe entirely to scientific research. It is no "simple," no plant or mineral which any one might gather and test as to its effects on human diseases. It is an artificial product created by the chemist, and its introduction to the pharmacopœia was not due to any random attempts to discover whether it might have some physiological activity, but to knowledge of its chemical reactions.

When Liebig, in 1830, prepared the first chloral, he was engaged on a purely chemical research, and had no thought of producing a useful medicine. The hydrate of chloral was soon after discovered, but, like chloral itself, remained for years merely a chemical curiosity. The sole interest and importance of chloral depended on the fact that it was an aldehyde in which three atoms of hydrogen were replaced by three atoms of chlorine, and on the light thus thrown on the chemical architecture of ethylic alcohol and its derivatives and allies.

As the chemists continued their work on chloral, seeking to unravel its molecular structure, it was discovered that when treated with alkalies it broke up into formic acid and chloroform. Physiological research having already proved that the circulating blood is feebly alkaline, it occurred to Liebreich, thirty years after the discovery of chloral, that this substance might be of therapeutic value: that by slowly giving off chloroform in the blood, it might act as a safe anæsthetic, and in cases where thorough anæsthetism was not desired might be useful in producing sleep. This was first tested on the lower animals, and the efficacy and safety of the drug being demonstrated on them, it was next administered to human beings, with what success you know.

Although it has now been ascertained that chloral hydrate does not split up in the blood as Liebreich supposed it might do, but circulates and acts as chloral, yet the fact remains that we owe our knowledge of its therapeutic value to scientific experiment.

What that value is may be stated in the words of Koehler: "Like opium, chloral hydrate is, and will continue, an indispensable agent for therapeutists of all future time."

Interesting as is the history of strychnine and chloral, still more so is that of *amyl nitrite*, a drug not yet officinal, but now being born, if I may use such a metaphor. The chemist has discovered it; the physiologist and pharmacologist have experimented with it; and now the practicing physician is testing it clinically. Whatever his ultimate decision be as to its greater or less value, its story serves well to illustrate how a new remedy is discovered, and how many sciences coöperate to add to the physician's armament.

More than forty years ago certain proprietors of vineyards in the south of France found that the brandy distilled from the "marc," the crushed residue of grapes whose juice had been expressed for wine making, had sometimes an unpleasant taste which greatly diminished its market value. This taste was found to be due to a greasy liquid, named *oil of marc*. They collected some of this oil and sent it to Balard, then Professor of Chemistry in the Faculty of Sciences, of Paris, asking him to study it, with the hope of learning how it might be separated from the brandy. The substance was already known to chemists, but was difficult to obtain. Hence Balard eagerly agreed to the request; to quote his words: "I assented very readily to this proposition, because it offered, for myself, an opportunity to obtain materials for a purely scientific research and for those who asked my advice some chance to improve the quality of a product which was the principal source of wealth in these districts."

On examining the "oil of marc" Balard found that its chief constituent was a substance already described by Dumas as *potato oil*. He soon arrived at the conclusion that it was an alcohol; but before his results were published this fact was discovered and announced by Cahours, who named the substance *amylic alcohol*. Cahours however did not go farther with its study, and so Balard took it up again; he examined the compounds which it might form, and, to still further elucidate its nature, the action upon it of oxidising agents; among these nitric acid naturally found a place. The combined action of nitric acid and heat gave rise to an ether, entirely analogous to the well known nitrous ether produced in like way from common alcohol, but with amyl instead of ethyl as its radicle. This substance was what we now name nitrite of amyl, and its discovery was announced by Balard in 1844. It remained for years something that merely interested chemists as throwing light on the nature and constitution of alcohols, as no one thought of testing it as a therapeutic agent.

In 1852 Claude Bernard discovered that section of the cervical sympathetic was followed by rise of temperature and dilatation of the blood-vessels on the same side of the head, and, following up this discovery, Brown-Sequard demonstrated that irritation of the sympathetic caused vascular constriction. Thus the vascular nerves were discovered; an advance in our knowledge of the physiology of the circulation second only to Harvey's great work.

Bit by bit the functions of the vaso-motor system were ascertained. Its main nerve-centre was located in the *medulla oblongata*, and it was found that in a variety of ways this centre could be aroused to abnormal activity; that if irritated it might so excite the nerves of the vessels as to cause extreme contraction of the muscular coats of the arterioles, and thus oppose great resistance to the flow of blood through them; in this way enormously raising aortic pressure and putting a great strain on the left ventricle of the heart. It was also demonstrated that destruction of the vaso-motor centre or section of the spinal cord (which put most vascular areas in the body beyond its control) was followed by dilatation of the arteries and a great fall in blood pressure. Thus we came to know that the nervous system and the muscular coats of the arteries played an active part in controlling the blood supply to various regions of the body; and that congestion or anæmia of any organ not only might be, but in most cases is due rather to abnormal activity of nerves or blood-vessels, than to changes in the work done by the heart. This fruitful idea was,

of course, soon seized by pathologists and applied in many cases with good results, to clearing our conceptions of diseases dependent on local vascular spasm or paralysis.

Years passed by and no one suggested that there might be a disease whose essential symptom was a convulsive activity, an epileptic fit, of the muscles of the arterioles in general.

In 1859, Guthrie* observed that amyl nitrite, when inhaled, caused flushing of the face, throbbing of the carotids, and a quickened heart-beat. Some years later (1865) Richardson called attention to this substance as an agent which might be useful, from its power of causing dilatation of the smaller arteries and capillaries.

Next Gamgee discovered by experiment on animals, that nitrite of amyl reduced arterial pressure to a remarkable extent, and Lauder Brunton, assisting at some of Gamgee's experiments, had this fact impressed on his mind.

So far we have chemistry, physiology and pharmacology coöperating; but to give us a therapeutic result pathology was needed.

Brunton lived day and night with a victim of *angina pectoris*: baffled and irritated by his ignorance of the nature of the disease, he strove in every way to get a knowledge of the proximate cause of its frightful symptoms. Marey had invented the sphygmograph for the purely physiological end of ascertaining the mode in which the blood flowed through the arteries, but it had been learned that this instrument could also afford information regarding intra-arterial pressure.

Brunton, making use of the sphygmograph, found that during a spasm of breast pang the intra-arterial tension was greatly increased: increased so much that the anguish of his patient might well be due to the resistance opposed to the systole of the left ventricle of the heart. Pondering on this fact, it occurred to him that the agony should, then, be relieved if the smaller arteries could be dilated. Brandy, ether, chloroform, ammonia, and other remedies had been used over and over again in similar cases and with little benefit. He thought of Gamgee's experiments with amyl nitrite, and his chief in the Edinburgh Infirmary, Dr. Hughes Bennett, gave him permission to try it; the result, stated in his own words, was,† "My hopes were completely fulfilled. On pouring from five to ten drops of the nitrite on a cloth and giving it to the patient to inhale, the physiological action took place in from thirty to sixty seconds, and simultaneously with the flushing of the face the pain entirely disap-

* Journ. Chem. Society, 1859.

† Lancet, 1867, Vol. II, p. 98.

peared. . . . Occasionally it began to return about five minutes after its first disappearance; but on giving a few drops more it again disappeared and did not return."

The subsequent pharmacological researches of Brunton, of Wood, of Amez Dioz have justified the therapeutic conception which led to the first administration of amyl nitrite, and have suggested its use, with good results, in other diseases whose prominent symptom is vaso-motor convulsions.

Although it may and does fail in certain cases, there still remains the fact that many men and women who lived in terror, never knowing when a spasm of angina pectoris might agonize them, now go about their daily duties in peace, because they carry with them a tiny phial of amyl nitrite. To quote the words of Wood, "It seems useless to speculate how the nitrite acts in many cases; but there is now abundant evidence of its value in relieving, almost instantly, agony which has resisted all other treatment."

I should only weary you were I to repeat the story of other valuable additions to the materia medica due to pharmacological and physiological research; it would be to most of you but an old tale. It is, moreover, hardly necessary to point out that the story of the past, thoughtfully read, is the safest guide for the future. When, bearing this story in mind, we think also of the activity of modern chemistry, especially on its synthetic side, and realize that almost daily there are created in the chemical laboratories of the world new compounds, whose action on the animal body may be as potent, and, in disease, as beneficial as that of chloral or strychnia; and that not one in a hundred of such compounds is now tested as to its possible therapeutic value: when we bear, I say, all these facts in mind, can there be any among us who does not feel eager to encourage and promote pharmacological research?

There are at present a small number of laboratories devoted entirely to such work on the continent of Europe; not one, I think, in the United States. Such investigations are of course often made here in physiological laboratories, but usually as a secondary matter and for purposes with no direct therapeutic end in view. I believe that as regards the advancement of medical art, there is nothing at present more desirable than an increase of well-equipped workshops, in which men already trained in chemistry, in physiology, in pathology, shall investigate the action of substances, with a view to discover whether they may be useful as medicines, and in what pathological conditions they may be rationally expected to prove of benefit.

Pharmacology depends on experiments on living animals. The whole history of the *materia medica* teaches that until such experiments were systematically made, drugs were selected and prescribed in accordance with erroneous and often fanciful notions. Its history also teaches that the action of no substance can be discovered by *a priori* reasoning. The attempt to do so leads only to such absurdities as the doctrine of signatures. The art of medicine advances by observation and experiment, rarely by accident.

Are we to experiment in the first case on men and women, or on the lower animals? It is incomprehensible that any one should hesitate as to the answer!

Test the new substance on the frog, on the rabbit, on the dog; and when we have thus gained a knowledge of the organs on which it acts and the mode in which it affects them, then, but not till then, try it on man. Repeated experience has taught us that in the vast majority of cases we may argue with much certainty from the influence of drugs on lower animals to their effect on human beings; therefore, we refuse to test first on man or woman a new remedy, though even the Bishop of Oxford and the editor of the *Spectator* protest that we have no right to sacrifice frogs or rabbits for the promotion of human welfare. To the physician, the preservation of human life is the most sacred of all duties. It is one to which all sentiments must yield, save those of truth and honor.

There is one great fallacy which invalidates most of the reasoning of the anti-vivisectionists. They assume that physical pain is the greatest of evils. Some of the more extreme among them maintain that we have no right to kill a dog to save a man's life! These need no answer; they belong to the great army of "cranks," and the common sense of mankind will render them harmless. By the remainder, those who dispute our right to make man happier at the expense of lower animals, the question is not stated so plainly. They maintain that we may not hurt an animal in order that we may save man from pain. Were this a fair and full statement of the case, some of us might hesitate before dissenting from their view of the matter. There *are* men in the world whose sufferings I might rather witness than inflict the same on a dog. But physical pain is, after all, a relatively trivial matter; it is disagreeable, and it is one of our greatest rewards to be able in many cases to remove or alleviate it; but it is by no means the worst of ills. Many persons gladly submit to it for some mere gain in personal appearance, as the removal of supernu-

merary hairs from the face, or the extraction of an unsightly tooth. Not merely do men and women themselves undergo very severe pain for such purposes, but they cause their children to submit to it; thus emphasizing their conviction that there are things much worse than physical suffering.

It is not mere physical suffering that we labor to diminish. We labor to save *life—human life* with all its ties. Were I to see a man tortured with facial neuralgia, and knew that I could relieve him by inflicting equal pain on a dog or horse, I hardly know what my decision would be. I suppose I should decide in favor of the man. But that is not the question which faces our profession in regard to experiments on animals; it is how we may better our knowledge and increase our power to save the life of husband and father—of wife and mother—of the child in whose life the hearts and hopes of its parents are bound.

Certain of our opponents have their sympathies greatly excited by the occasional cry of a dog enduring pain from pharmacological experiment. Have they listened to the wail of the new-made widow? Some of them use their fiercest invective to calumniate those who have kept animals alive a few days after an experiment, that the causation of disease may be better understood and its prevention made possible. Have they realized the years of penury and misery too often the lot of the orphan? They have not felt personal responsibility for the life of the bread-winner, or they would surely say with us, kill a hundred, kill a thousand animals if you have any reasonable hope of thereby preserving to one wife her husband, to one child its mother.

The history of experimental pharmacology teaches us that we have abundant ground for such hope.

No doubt many of you have sat up all night with a patient dying of tetanus—have seen convulsion follow convulsion and feared each one would be the last, yet almost hoped so, that the suffering might end. I shall never forget the night I spent by such a bedside. Harrowed by the agony before me, convinced that abnormal excitability of the gray matter of the spinal cord was its cause; certain that there was some drug, if I only knew it, which could act specifically on the nerve cells of this gray matter and paralyze them long enough to give the system a chance to overcome the disease: reduced to despair, and suffering perhaps as much as the patient before me, from the torturing consciousness of my ignorant impotence—I felt then and feel now that this man's life should have been spared to his wife and children. We knew what the disease was;

more earnest pharmacological research could and would have taught its cure.

As we look around, we see the fields white for the harvest. Is life or death to reap them? Truly the laborers are few, and if we toil not day and night to increase our knowledge and power to prevent and heal disease, the crop will nevertheless be garnered: a ghastly reaper who gathers where he has not strewn will be tirelessly at work, and his name is—premature death.

To those who impede our work we answer: look around you and see the daily suffering due to disease. We are striving, and with greater success each year, to control and to diminish it; you can help us if you will; you can use your influence to insure that sanitary laws be known and obeyed; that the hungry child has wholesome food; that the laborer shall not arise each morning so enervated by sleeping in an overcrowded room as to be driven to drink.

When through your efforts in such direction, supplemented by our investigations, it comes to pass that human disease no longer exists, and death is known only as the result of accident or old age, *then* we may listen to you if you ask us not to experiment on the lower animals. Until then we close our ears to your protests and, looking neither to the right nor left, press onward!

XXI.

SOME THOUGHTS ABOUT LABORATORIES.

ADDRESS DELIVERED AT THE OPENING OF THE HOAGLAND LABORATORY,
BROOKLYN, DECEMBER 15, 1888.

[*Brooklyn Medical Journal*, February, 1889.]

From the point of view of investigators and teachers of the biological sciences, this may be designated the age of public laboratories.

There is indeed evidence that in Egypt, under the rule of the earlier and greater Ptolemies, there existed in Alexandria and were supported by the State, schools of instruction and research in the practical direct study of anatomy, physiology and pathology; as well as great libraries in which every student could learn what had already been done or thought in his own department of study. But with the degeneracy of the later Ptolemies and the subjugation of Egypt by Rome, all that was good left Alexandrian science; the great museum became simply a place in which ceaseless metaphysical guesses and theories, barren of everything but bitter quarrels, took the place of the faithful and patient study of man and the rest of nature. Before the Christian era the Alexandrian school had almost ceased to be of any value to humanity.

From that time until sixty years ago there was not a single public laboratory for scientific study in the world; that is to say, a laboratory open to all competent workers on easy terms, and provided with books, instruments, and skilled assistants.

To-day such laboratories girdle the earth from Tomsok to Tokio—from Siberia westward to Japan. They are to be counted by the hundred, and States vie in building them and making each new one more complete, and even architecturally more splendid than its rivals. One of the first things Germany did after the wars which welded her into a great empire was to build laboratories—palaces of science they have been called—in Berlin and Strasburg.

In this country the building and endowment of laboratories has for most part been attained in a far better way—by private generosity, rather than by public subsidy, combined, as it must be, with government

control. Science cannot for any long period advance safely in chains, even if those chains be golden. There lurks as much danger to progress in an established national science as in an established national church.

This danger is illustrated by the comparative deadness of French science during the last forty or fifty years, in which it has been directed from a government office and centralized under bureaucratic control; and even in victorious Germany, now that the various States are consolidated into one empire, every detail of which is controlled from Berlin, many leaders of German science, especially among the younger men of talent and genius, are beginning to dread the outcome as regards the intellectual life, freedom and vigor of the empire. Political questions influence the appointment of university professors, and such influence cannot but be injurious.

In these United States there is no such danger. The National Government needs the services of scientific experts in order to protect the health and promote the material prosperity of its citizens, to undertake great geological surveys, or the investigation of the life habits of insects injurious to agriculture, or the study of the breeding-places and habits of food-fishes and of their enemies, or to promote artificial fish-culture; even from time to time to undertake, not merely for a prospective or immediate material gain, but for national credit and renown, great enterprises on purely scientific grounds, such as expeditions to observe solar eclipses or Arctic expeditions. For all such purposes it has, and has had, at its disposal, the best qualified scientific men in the country and it gets their services very cheap.

But, in addition to national scientific enterprises, as a supplement (perhaps in some sense as a corrective) to them, we need independent scientific research and facilities for it. And it may be interesting to consider how we, the American people, are solving the problem of the due promotion of scientific education and research by the government, while at the same time securing opportunities for independent thought and investigation.

The problem is being solved, *has* been solved, by the liberality of private citizens. While promoting the investigation of scientific questions by the ruling powers, they have also built and endowed laboratories, colleges and universities. They have provided rooms and appliances for study and research, in which no earnest student can be repressed or suppressed because his ideas are new or in conflict with those adopted by the officials of a central government bureau. Through such private endow-

ments—trusts as they are for the public welfare, numerous and generous—American science promises to attain a variety and independence of thought such as no national science has ever had in the past. Its characteristic is that it is individual—it is democratic. With a solid background of traditions and established ideas, it has a liberty which does not often degenerate into license; and all history teaches that such a combination is that which leads most quickly to human progress.

American science works not for the glory of a monarch, as Alexandrian science for the fame of Ptolemy Soter. Neither does it strive to promote the interests of an aristocracy, nor to fill the pockets of a plutocracy. Some such consequence may now and then follow its advance, but only as a by-result of its general contribution to the national welfare. It exists by the people and for the people. To make human life longer and healthier and happier is the result, as it is the aim of modern science: to discover truths and to apply them to the welfare of mankind.

It is frequently asserted, and generally believed, that the first public laboratory for teaching and research was organized and set at work by the great chemist Liebig; but this is an error. The merit belongs to Purkinje. Liebig's effort was no doubt far better supported financially, more ambitious, and more widely known; but some years before the foundation, in 1826, of Liebig's celebrated laboratory at Giessen, which is claimed as the parent of all modern laboratories, Purkinje had provided means for students to study physiology and pathology practically, to examine the working of the body in health and disease—the very subjects for whose investigation the Hoagland laboratory has been built, equipped and endowed. To every physiologist present, the name of Purkinje will call up some remembrance of the man of genius who first paid attention to the retinal images of his own blood-vessels, images ever since known as Purkinje's figures; of the man who first described the peculiar sensations of vertigo produced by rotation of the body, and attempted to explain them; of the man who is the father of psycho-physics and physico-physiology; of the man who discovered the germinal vesicle of the ovum. Such achievements are glory enough; but to all the other fertile work of Purkinje we must in justice add the foundation of the first public laboratory (in the modern sense of the term) after the Christian era. Liebig's deserved repute and fame need no factitious prop; and as to the question who founded the first public laboratory, we need, I trust, have no quarrel with our friends the chemists. The emulation is but an evidence of the belief of all students and fosterers of science in the

value of public laboratories. That the merit of having first organized them is eagerly claimed is a proof of their public utility. Our country believes in its laboratories, and its citizens provide them.

Purkinje's laboratory was but ill equipped; it was supported at first by his private purse, afterwards by voluntary contributions from his friends. No doubt its space was cramped, its apparatus scant, its general facilities for work very limited. Thanks to the liberality and patriotism of Dr. Hoagland, we are to-night celebrating the formal opening of a laboratory with abundant space, comfortable workrooms, an excellent library, the best apparatus that has been invented, skilled teachers and assistants, and with all else that may contribute to advance knowledge as to the workings of our bodies and the laws which govern them in health and disease. It is founded to increase human knowledge in regard to the *sciences* of physiology and pathology, and the *arts* of medicine, surgery and hygiene.

On such an occasion it is meet that we gratefully recall Purkinje's work—the little germ from which this great laboratory has sprung and which gives us a direct and glorious ancestry, while also entitling us to feel some sort of parental pride in the great laboratories of physics and chemistry now to be found wherever civilization is firmly established.

The public-laboratory idea started by Purkinje and Liebig did not quickly spread. Bacon had long before pointed out the necessity of experiments in the study of nature; but naturalists, for the most part, had still enough to do in the mere direct observation of the phenomena exhibited by plants and animals under the conditions of their normal daily life and under circumstances of disease or accident. There were scattered here and there a few good experimenters; but the majority of biologists were usefully busy in simply seeing accurately under natural conditions; and very excellent observers many of them were.

It came at last to be realized that mere simple external observation of animals, though a fundamental first stage towards a knowledge of physiology and pathology, did not lead far; that it required to be supplemented by experiment. The majority of vital phenomena take place inside organisms, and therefore could only be observed by subjecting the animal to injuries, such, for example, as opening cavities of the body, in order to see the inner parts at work. The earlier experiments were mainly the removal of such hindrances to direct observation. The thoracic cavity was opened to see the beat of the heart; or the abdominal, to observe the movements of the intestines. Soon the range of expe-

riment was widened; it became obvious that in biology, as in other natural sciences, to know Nature and her ways we must cross-examine her by the Baconian method, putting her to work under conditions which could be varied at will by the observer, or, as he now became, the experimenter.

As an illustration, let me take such a common phenomenon as the movements produced by shortening of the muscles. Dissection of the dead body had taught that muscles were connected by means of nerves with the brain, and observation of cases of disease or accident had proved that a muscle immediately ceased to work when its nerve was seriously injured or was divided. Such direct observation led naturally to the conclusion that every muscle got its power or strength from the nerve, which thus came to be regarded as a sort of conduit carrying force or energy to the muscle from the brain. This erroneous notion was only upset by experiment added to observation. When it was found that the muscle of a living or recently killed animal, after section of its nerve, did still contract powerfully when excited by blows or by ammonia, by heat or by electricity, it became clear that the power of energy exerted by a working muscle resided in itself, and was not something carried to it by the nerve from the brain; that all which the nerve did was to set free or liberate energy already stored in the muscle, just as several other natural forces might do; the nerve, like them, merely pulled the trigger and discharged explosive material already present in the muscle fibres. Thus our whole conception as to the physiological relations of the nervous and the muscular systems was corrected.

It is needless to multiply instances. At present nearly every organ and liquid of the animal body has been isolated from the rest and its properties studied under the most varied conditions. It is not too much to say that most of what is real and substantial in our knowledge of physiology, and most of our similar knowledge in pathology, is based on such experiments.

Researches of value need for their successful prosecution buildings adapted for them, numerous assistants, and (in addition to the outfit of laboratories of physics and of chemistry) many pieces of apparatus specially constructed for physiological and pathological purposes.

Another reason why laboratories are necessary is the improvement in methods of teaching during late years; we no longer believe that any natural science can be taught successfully by words alone, even by the most learned and eloquent professor. When the conditions are such that

the students cannot make experiments themselves, we insist that they shall at the least have shown to them the most important facts; that the lecture and the text-book shall have as their accompaniment, I might perhaps say as their basis, actual demonstrations, supplemented if possible by personal experimentation by the learner himself. We ridicule the notion of any real teaching of physiology to a student who has never seen a beating heart, a blood-pressure experiment, a demonstration of the action of saliva on starch; of teaching pathology to those who have had no opportunity to observe the phenomena of inflammation with the aid of the microscope; of teaching bacteriology in its relations to disease to students who have never seen a bacillus, or had any ocular demonstration of its life-history, or of the fundamental phenomena of fermentation and putrefaction.

Many of us can remember the time when all the practical instruction a medical student obtained was in the dissecting-room and the hospital wards. One outcome of that state of affairs was in the medical schools a very undue amount of time and energy spent in the study of minutiae of human anatomy; but the best teachers recognized that the men must have some practical training, and the dissecting-room was in those days the only means of providing it. Medicine and surgery are advancing slowly but surely, and within the last twenty years with greatly increased velocity, from an empirical to a rational basis, both as regards the cure and, what is infinitely more important, the prevention of disease. Now that physiology, pathology and hygiene are being yearly more firmly established on general scientific principles, and have so perfected their methods that fundamental facts in those sciences can be easily demonstrated to medical students (or even investigated by them), the dominant rôle which gross anatomy has often hitherto had in medical education will be lessened, and the student will get more and more of his practical training through experimental physiology and pathology and hygiene. To permit and encourage this most important advance in medical education, such laboratories as the Hoagland must be provided and sustained by enlightened and public-spirited men.

It is interesting to glance backward and see how slowly the idea evolved and put in action by Purkinje and Liebig took hold—at any rate as regards physiology and pathology. Fifteen years after Purkinje's effort, the practical teaching of physiology and pathology amounted to almost nothing. Partly, no doubt, because the essential independence of those realms of human thought and inquiry had not been recognized. These

sciences were still regarded as mere accessories, more or less (perhaps on the whole less) helpful in the study of medicine and surgery; they were generally considered as only worthy of attention because of their possible use in connection with the medical arts, and were for the most part taught in conjunction with other subjects by a single professor. The greatest physiologist of his time, and one of the greatest of all time, Johannes Mueller, was in 1840 professor in Berlin of human anatomy, comparative anatomy, pathological anatomy, physiology, and embryology. That pathology is as distinct from pathological anatomy as physiology is from normal anatomy had not then been recognized, or another title would have been added to the list of Mueller's duties.

Among Mueller's students was Du Bois Reymond, now professor of physiology in Berlin. It is interesting to read his account of the small facilities for observation and practical work afforded in 1840 to students of scientific medicine under the greatest teacher of that time. He says:

"We were shown a few fresh specimens under the microscope, the art of putting up permanent preparations being still unknown. We had also opportunity to see the circulation of the blood in the frog's web" (something which every science student in every well conducted normal school in this country now sees without considering it any great matter). He goes on to say that he and his fellows saw the experiment of filtering frog's blood so as to retain the corpuscles and let the plasma through, and the resultant demonstration by the clotting of the colorless plasma, that the red corpuscles of the blood were not an essential element of the clot; he also had opportunity to observe an experiment in artificial digestion; one on section of the spinal nerve roots; a demonstration on reflex movements; and an experiment in pharmacology, proving that opium poisoning was not transmitted centripetally through the nerves. There was in the whole course but one demonstration on a warm-blooded animal, namely, section of both vagi, to show the resulting disturbance of respiration. That the pneumogastric nerves had any influence on the heart beat was still unknown. These half a dozen demonstrations were all the quasi-practical teaching that the student of physiology or pharmacology received in the best schools in 1840. That he should put up microscopic preparations himself or make an experiment himself were things hardly dreamed of.

Moreover, lecture diagrams were not in use. Du Bois Reymond states that he first saw them employed in England, and that he introduced them to Berlin in 1850.

It is, then, very clear that but fifty years ago appliances and methods for teaching histology, physiology, and pathology were very imperfect. We may next ask, how was it as regards facilities for research? The answer is that there were none. "Did a young man desire to institute a physiological research, he had for the most part to work in his lodgings, where on account of his frogs and rabbits he got into trouble with the people who kept the boarding-house, and where many experiments were quite impossible, or could only be carried out under the most adverse circumstances. No skilled assistants directed the young investigator's work; no library was accessible to him; no collection of apparatus gave him its precious aid. He had to buy his own books of reference and provide his own apparatus, often to make the latter himself." The student who undertook a research in those days rolled his induction coils, soldered his galvanic element, even made his rubber tubing, for that essential in every modern laboratory was not yet an article of commerce.

Some few men, those born to be physiologists, pathologists or pharmacologists, surmounted the difficulties. We need only call to mind the names of Du Bois Reymond, Ludwig, Brücke, Helmholtz, Vierordt, Donders, Bernard and others of their contemporaries. There was a good side to all this difficulty. Only earnest students would surmount them and undertake biological research. Whatever was done was done by a man who had his heart in his work, and who had to work so hard to do it that when his research was completed it was almost certain to be of importance.

No one believes in laboratories more thoroughly than do I; they are to-day among the institutions most essential for the increase of man's control over nature and his power to harness her as his servant, his drudge—instead of master. Nevertheless the great conveniences afforded by modern laboratories sometimes lead to their abuse. It has become so easy, in fact such a pleasant amusement, to make a so-called research that a great deal of it comes from the hands of sciolists. It may seem hard to designate as trash a considerable percentage of the work now issued from biological laboratories, but there is no other way of honestly stating its value. Incompetent and imperfectly trained persons are almost daily publishing so-called researches, the reading of which is pure weariness of spirit; and yet the physiologist or pathologist has to work his way painfully through them, in the hope that he may extract one grain from the bushel of straw. If I thought any considerable number of

trivial or plagiarized "researches" would be the outcome of this laboratory, I could not honestly congratulate you on its foundation ; but supervised by its founder, and directed by thoroughly competent men, I have no such fear. No triflers will be allowed to continue their trifling in it ; and what it may publish will be the outcome of earnest and faithful and thoughtful work.

When I entered this room to-night and saw you all here, eager to inspect the Hoagland Laboratory, the query which presented itself to me was, What went ye out for to see ? A reed shaken by the wind ? Those clad in soft clothing ? A prophetic or more than prophetic building ? Is this laboratory to be but a mere transient and unimportant element in the intellectual life of your city ? Is it to be but a place in which some teachers may live idly as those who dwell in king's palaces ? Or is it to be the seat and the training-place of prophets and more than prophets, from whom intellectual fire and enthusiasm shall spread over our nation ?

These questions it is mainly for you, men and women of Brooklyn, to decide. The best equipped laboratory, the most devoted teachers, are almost impotent unless they have the active sympathy and support of the community in which they are placed.

I appeal to you, citizens of no mean city—one known the world over as the City of Churches—and I speak with all sincerity when I urge you to cherish this laboratory as a new church. It is a temple for the study of the works of God, and to my mind as sacred a place as that in which you may meet to study the word of God.

Cherish it, foster it, keep its ideals high, so that as year follows year it shall become more and more a centre from which shall spread not only vast gains in our knowledge of the laws of health and in our power to conquer disease, but examples of single-hearted devotion to all that is true and noble and patriotic.

